DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1987

HEARINGS

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS

HOUSE OF REPRESENTATIVES

NINETY-NINTH CONGRESS

SECOND SESSION

SUBCOMMITTEE ON THE DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES

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DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1987

MONDAY, MARCH 10, 1986.

NATIONAL INSTITUTES OF HEALTH

OVERVIEW

WITNESSES

DR. JAMES B. WYNGAARDEN, DIRECTOR, NIH

DR. THOMAS E. MALONE, DEPUTY DIRECTOR, NIH

DR. WILLIAM F. RAUB, DEPUTY DIRECTOR FOR EXTRAMURAL RESEARCH AND TRAINING, NIH

NORMAN D. MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NIH

DR. ANTHONY S. FAUCI, DIRECTOR, NIAID, AND NIH AIDS COORDINATOR

DENNIS P. WILLIAMS, ACTING DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

OPENING REMARKS

Mr. NATCHER. At this time, we take up the budget request for our National Institutes of Health, and we have before the committee our Director of the National Institutes of Health, Dr. James B. Wyngaarden.

Doctor, it is a pleasure to have you back before the committee. You have appeared on a number of occasions, and before you give us your statement, tell us who you have with you at the table there, Doctor.

Dr. WYNGAARDEN. Thank you, Mr. Chairman.

With me today are Dr. Thomas Malone, Deputy Director; Dr. William Raub, Deputy Director for Extramural Research and Training; Norman Mansfield, Director of the Division of Financial Management; Dr. Anthony Fauci, Coordinator for AIDS Research, and Director of NIAID; and Mr. Dennis Williams, Acting Deputy Assistant Secretary, Budget, DHHS.

Mr. NATCHER. Dr. Wyngaarden, we will be pleased to hear from you at this time.

BUDGET REQUEST FOR NIH

Dr. WYNGAARDEN. Mr. Chairman, it is my privilege to present the President's budget proposal for the National Institutes of Health for fiscal year 1987, and to outline briefly our activities and plans.

In doing so, I wish to add a personal observation that, during the time I have been Director of the National Institutes of Health, I have been impressed by the care with which you, your colleagues, and the staff of the Subcommittee deal with matters affecting the National Institutes of Health.

NIH CENTENNIAL

Fiscal 1987 will be observed as NIH's centennial year. We see the NIH centennial as much more than an institutional birthday, but rather as an occasion for creating a better understanding among the American people of the importance of biomedical research—an opportunity to convey a sense of its accomplishments and promise.

RESEARCH ACCOMPLISHMENTS

In my prepared remarks, I have included several pages of the accomplishments of the last year or two. I have included reference to advances against AIDS, highlighting basic advances in the development of treatment agents and progress toward the development of a vaccine; in addition, I have cited the development of AIDS screening tests for donated blood. The blood supply now is virtually safe, and the risk from hemophilia treatment products is essentially eliminated.

I also cited Dr. Rosenberg's accomplishments in cancer therapy, with a new approach announced and under way this past year.

I have cited progress toward certain genetic diseases, including the discovery of a marker for cystic fibrosis, and another for Duchenne muscular dystrophy.

I cited progress in diabetes research toward cataract control, and further progress in the perfection of donor pancreas islet cell transplants.

There is growing concern about the rising costs of health care and the impact of biomedical research on those costs. You will be interested in a survey recently conducted at the NIH looking at recent examples of advances in biomedical research that have reduced health care costs. A selection of 12 such advances were estimated to save about $2.5 billion annually in health care costs.

Three examples are in the text: drug treatment rather than surgery for patent ductus arteriosus, a serious heart defect of infants; drug treatment of coronary artery disease instead of coronary bypass surgery in certain patients; and newly developed laser treatment for serious eye diseases.

ADJUSTMENTS TO FY 1986 APPROPRIATION

Mr. Chairman, we understand the need for strong measures to reduce the Federal deficit. The budget we present is an example of the kind of restraint the times require of the non-exempt components of the Government.

At the same time, we are well aware of the potential impact of the fiscal year 1987 request, and will do our best to maintain the stability of the Nation's biomedical research enterprise and the momentum of its recent progress. To do so will require maximum flexibility so that we can make maximum use of our resources to take advantage of scientific opportunities.

It is necessary to take into account certain adjustments in the fiscal year 1986 budget. The first such modification is a reduction of $236.2 million, as required by the Balanced Budget and Emergency Deficit Control Act.

This 4.3-percent decrease has been applied uniformly against the appropriation of each NIH Institute, as well as against each research mechanism and each identified program, project, or activity.

In addition, three rescissions are proposed, totaling $76.8 million in fiscal year 1986 budget authority. These rescissions call for a decrease of $53.7 million from research project grants as part of a new stabilization policy, a decrease of $13.9 million appropriated to the Office of the Director for AIDS research, and a decrease of $9.1 million from the small and minority universities and colleges programs.

The reduction in project grants is a necessary transition to the spending levels in the 1987 President's budget. The small and minority schools programs will be continued at the fiscal year 1985 level.

FY 1987 BUDGET REQUEST

The fiscal year 1987 budget request for NIH is $4,936,157,000, a decrease of $131,206,000, or 2.6 percent from $5,067,363,000, which is the comparable fiscal year 1986 total after deducting for the Balanced Budget Act and the fiscal year 1986 proposed rescissions.

With this presentation of the fiscal year 1987 budget, the Administration proposes a new research grant stabilization policy. Under this new policy, the total number of NIH research project grants would be stabilized at a total of 18,000 grants.

Almost 57 percent of the total proposed NIH budget is allocated for such grants. This is a departure from the previous stabilization policy where the goal was to stabilize the number of competing grants.

Thus, the fiscal year 1987 request would include support for 18,000 grants, of which 5,140 would be competing awards. This compares with 18,357 total grants awarded in fiscal year 1985 and 18,195 such awards projected for fiscal year 1986.

A new method of reimbursing grantees for the indirect cost portion of NIH grant awards is assumed with the fiscal year 1987 budget. This proposal reflects the commonly expressed concerns of both the Congress and the Administration over the escalating costs of research.

The new "Fair Share Allocated Overhead Policy" would set a national maximum limit for academic grantees on the reimbursement rate for the administrative overhead costs that constitute approximately one-half of all indirect cost reimbursements to these institutions.

Beginning in fiscal year 1987, the new policy would cap reimbursement for such administration at 20 percent of the grant's direct costs, as compared with the current average of 26 percent for this cost element. Implementation of the new policy is expected to reduce indirect costs by an estimated $85 million.

The request for $198.2 million for research training will support about 9,250 predoctoral and postdoctoral trainees, a reduction of 700 trainees from the proposed fiscal year 1986 level of 9,950.

The number of research centers in fiscal year 1987 would be decreased by 11 to a total of 523.

Other extramural NIH research mechanisms will be maintained at approximately their fiscal year 1986 funding levels.

Two exceptions are the Biomedical Research Support Grant Program and the Extramural Facilities Construction Programs, both of which will be eliminated due to budgetary constraints and the relatively lower priority of these programs.

Intramural research at the NIH in 1987 would be funded at $548.4 million, an increase of $11.5 million or 2 percent above the comparable fiscal year 1986 level.

The fiscal year 1987 budget request for NIH excludes all funding related to acquired immunodeficiency syndrome, or AIDS. All fiscal year 1987 resources for AIDS are being requested for appropriation to a single account in the Office of the Assistant Secretary for Health, who will have the responsibility to allocate these funds to the several PHS agencies participating in AIDS research, prevention, and treatment. Estimates of the number of NIH research project grants on AIDS, to be supported from the OASH fund, are included in the number of grants counted against the stabilization objective.

In closing, permit me to call attention to the fiscal year 1987 budget proposal for the National Institute for Arthritis, Musculoskeletal and Skin Diseases. Details regarding the planned activities of the new Institute will be presented later in the hearings.

I believe the committee will also be interested in knowing that the Public Health Service is developing an implementation plan for the establishment of the National Center for Nursing Research at the NIH.

I will be pleased to answer any questions you may have.

[The statement of Dr. Wyngaarden follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institutes of Health

Mr. Chairman, it is my privilege to present the President's budget proposal for the National Institutes of Health (NIH) for Fiscal Year 1987, and to outline briefly our activities and plans. In doing so, I wish to add a personal observation that during the time I have been Director of the National Institutes of Health, I have been impressed by the level of interest and understanding with which you, your colleagues, and the staff of the Subcommittee deal with matters affecting the National Institutes of Health.

Fiscal 1987 will be observed as NIH's centennial year. In August of 1887, the one-room National Laboratory of Hygiene was opened at the Marine Hospital on Staten Island to study cholera and other infectious diseases, hoping that from the research could be found the means for fighting such devastating diseases. Thus began what is described in our centennial slogan as "A Century of Science for Health." For after several changes in name as well as location, the National Laboratory of Hygiene became the National Institutes of Health.

American science in the 1880s was rooted in the work and inspiration of the European giants Robert Koch and Louis Pasteur. It is fortuitous that the centennial of the Pasteur Institute coincides with that of the NIH. In May of the next year, Pasteur and the NIH will hold a symposium on molecular biology in Bethesda as a joint celebration of this important anniversary. Other centennial events are scheduled at various times during the year, including regional salutes to the federal/academic partnership in biomedical research so successfully nurtured by the NIH. These locally sponsored celebrations will be held in such centers of research as Boston, St. Louis, Atlanta, and San Francisco. We see the NIH centennial as much more than an institutional birthday, but rather as an occasion for creating a better understanding among the American people of the importance of biomedical research--an opportunity to convey a sense of its accomplishments and promise.

Among those accomplishments are tremendous advances against acquired immune deficiency syndrome (AIDS). Special attention is being given to involving additional scientific groups and additional AIDS patients in these efforts. The National Cancer Institute and the National Institute of Allergy and Infectious Diseases (NIAID) are planning to fund National Cooperative Drug Discovery Groups, aimed at discovery of effective agents to interfere with replication of the AIDS virus and at restoration or maintenance of the immune response. The NIAID also plans to establish AIDS Treatment Evaluation Units in various locations for the testing of antivirals, immune modulators, and antibiotics in AIDS patients. At the same time, NIH intramural and grant-supported scientists are actively pursuing a variety of scientific approaches to the development of vaccines.

Simultaneously, we are learning a great deal more about the basic structure of the virus itself, how it controls its replication, how it destroys certain target cells. These new insights may prove crucial to the eventual discovery of effective agents for prevention and treatment of AIDS.

The AIDS screening test for donated blood, based on the work of Dr. Robert Gallo of the National Cancer Institute, has provided a means for safegarding hemophiliacs from AIDS. This test and development of a method for pre-treating Factor VIII against HTLV-III has resulted in a remarkable reduction in risk for hemophiliacs. Studies have shown that in some hemophilia populations over 90 percent of hemophiliacs had developed antibodies to HTLV-III. Several recent studies show that of hemophiliacs who had received only treated Factor VIII, none has developed antibodies to the AIDS-causing virus.

An NCI research team, led by Dr. Steven Rosenberg, has developed a new approach to cancer treatment using interleukin-2 to activate the immune system to destroy cancer cells. The original study in 25 patients has been expanded through funding at 6 medical centers where about 300 additional patients will be treated.

Researchers are making gains against genetic diseases. Recently, NIH scientists, working with investigators elsewhere, found a genetic marker for cystic fibrosis, the most common fatal inherited disease of Caucasians. This discovery permits the identification of most carriers of the disease within families having a history of the disease, and brings scientists closer to finding the gene itself and to discovering the basic defect causing cystic fibrosis. Another major advance has been made in understanding of the genetic neuromuscular disease Duchenne muscular dystrophy (DMD). Scientists have recently cloned a DNA fragment that detects a defect in or near the DMD gene. This work forms the basis for much more accurate detection of female carriers of the gene and for prenatal diagnosis.

Great strides are also being made against the complications of diabetes. Scientists are beginning to understand the role of the enzyme aldose reductase in the development of the cataracts common in diabetes. This research has led to the evaluation of aldose reductase inhibitors--drugs now being tested in clinical trials for the prevention of diabetic eye disease and other complications as well. Research has provided other new treatment options and new hope for the individual at risk for the most serious complications of diabetes. Examples include laser treatment for diabetic retinopathy and improvements in kidney dialysis. Another treatment approach, transplantation of donor pancreas islet cells to replace those lost in diabetes, is progressing with exciting rapidity. Such transplantation of pancreas tissue offers great hope for providing recipients with a close facsimile of the normal function of the pancreas.

As you know, there is growing concern about the rising costs of health care and the impact of biomedical research on these costs. Undeniably, certain fruits of research--especially technological advances--initially may appear to increase health care costs. You will perhaps be interested in an informal survey we recently conducted at the NIH looking for examples of advances in biomedical research that have reduced health care costs. A selection of just 12 recent advances were estimated to save about $2.5 billion annually in health care costs. Among these examples were drug treatment rather than surgery for patent ductus arteriosus, a serious heart defect of infants; drug treatment of coronary artery disease instead of coronary bypass surgery in certain patients; and newly developed laser treatment for serious eye diseases.

Mr. Chairman, we understand the need for strong measures to reduce the federal deficit. The budget we present is an example of the kind of restraint the times require of the non-exempt components of the Government. At the same time, we are well aware of the potential impact of the FY 1987 request and will do our best to maintain the stability of the Nation's biomedical research enterprise and the momentum of its recent progress. To do so will require maximum flexibility so that we can make maximum use of our resources to take advantage of scientific opportunities.

Before proceeding to a discussion of the FY 1987 proposal, however, it is necessary to take into account certain adjustments in the FY 1986 budget. The first such modification is a reduction of $236.2 million, as required by the Balanced Budget and Emergency Deficit Control Act. This 4.3 percent decrease has been applied uniformly against the appropriation of each NIH institute, as well as against each research mechanism at the NIH aggregate level, and each identified program, project or activity. In addition, three rescissions are proposed totaling $76.8 million in FY 1986 budget authority. These rescissions call for a decrease of $53.7 million from research project grants as part of a new stabilization policy, a decrease of $13.9 million appropriated to the Office of the Director for AIDS research, and a decrease of $9.1 million from the small and minority universities and colleges programs. The reduction in project grants is a necessary transition to the spending levels in the 1987 President's budget. The small and minority schools programs will be continued at the FY 1985 level.

The FY 1987 budget request for NIH is $4,936,157,000, a decrease of $131,206,000 or 2.6 percent from $5,067,363,000 which is the comparable FY 1986 total after deducting for the Balanced Budget Act and the FY 1986 proposed rescissions.

With this presentation of the FY 1987 budget the Administration proposes a new research grant stabilization policy. Under this new policy the total number of NIH research project grants would be stabilized at a total of 18,000 grants. Almost 57 percent of the total proposed NIH budget is allocated for such grants. This is a departure from the previous stabilization policy where the goal was to stabilize the number of competing grants. Thus the FY 1987 request would include support for 18,000 grants of which 5,140 would be competing awards. This compares with 18,357 total grants awarded in FY 1985 and 18,195 such awards projected for FY 1986.

A new method of reimbursing grantees for the indirect cost portion of NIH grant awards is assumed with the FY 1987 budget. This proposal reflects the commonly expressed concerns of both the Congress and the Administration over the escalating costs of research. The new "Fair Share Allocated Overhead Policy" would set a national maximum limit for academic grantees on the reimbursement rate for the administrative overhead costs that constitute approximately one-half of all indirect cost reimbursements to these institutions. Beginning in FY 1987, the new policy would cap reimbursement for such administration at 20 percent of the grant's direct costs, as compared with the current average of 26 percent for this cost element. Implementation of the new policy is expected to reduce indirect costs by an estimated $85 million.

The request for $198.2 million for research training will support about 9,250 predoctoral and postdoctoral trainees--a reduction of 700 trainees from the proposed FY 1986 level of 9,950. The number of research centers in FY 1987 would be decreased by 11 to a total of 523 and the funding for the centers would be reduced by an aggregate of 4 percent from the 1986 funding level.

Other extramural NIH research mechanisms will be maintained at approximately their FY 1986 funding levels. Two exceptions are the Biomedical Research Support Grant (BRSG) Program and the Extramural Facilities Construction Programs, both of which will be eliminated in FY 1987. Because of the continued emphasis on investigator-initiated project grants as the most appropriate form of support, and in the face of growing concern over budget restraints, the BRSG must rank as a lower priority when compared with other NIH programs. The Extramural Facilities Construction Program is also proposed for elimination due to budgetary constraints and the relatively lower priority of this program. Intramural research at the NIH in 1987 would be funded at $548.4 million, an increase of $11.5 million or 2 percent above the comparable FY 1986 level.

The FY 1987 budget request for NIH excludes all funding related to acquired immune deficiency syndrome (AIDS). All FY 1987 resources for AIDS are being requested for appropriation to a single account in the Office of the Assistant Secretary for Health (OASH), who will have the responsibility to allocate these funds to the several PHS agencies participating in AIDS research, prevention, and treatment. Estimates of the number of NIH research project grants on AIDS, to be supported from the OASH fund, are included in the numbers of grants counted against the stabilization objective.

In closing, permit me to call attention to the FY 1987 budget proposal for the National Institute for Arthritis, Musculoskeletal and Skin Diseases. Details regarding the planned activities of the new institute will be presented later in the hearings. I believe the committee will also be interested in knowing that the Public Health Service is developing an implementation plan for the establishment of the National Center for Nursing Research at the NIH.

I will be pleased to answer any questions you may have.

APPROPRIATIONS HISTORY

Mr. **Natcher**. Thank you, Doctor.

As you have heard me say on more than one occasion, when I was first elected a Member of Congress, we had for the NIH appropriation the sum of $71,153,000.

The year I was elected to the Committee on Appropriations, the appropriation for NIH was $77 million. As you know, we are up now to a little over $5.1 billion, and that figure is all right, Dr. Wyngaarden. Here is where we ought to spend our money.

On this subcommittee, we have believed for a long time in the support of biomedical research, and from time to time, we ask witnesses to appear before our committee to talk to us about biomedical research. This bill has had its ups and downs down through the years.

Doctor, from 1970 to 1976, bills reported from this subcommittee were vetoed seven times. We overrode three times, and we failed three times. One time was a pocket veto.

I guess maybe if you checked, you would find that this bill has been vetoed more times during the 20th century consecutively than any other appropriations bill, and at the same time, Dr. Wyngaarden, this is the most important appropriations bill that goes through the Congress.

We had a distinguished gentleman from Ohio who served on our committee by the name of Mike Kirwan, and my friends on the committee remember him well. He used to call this bill, and one or two others, the People's Bill. That terminology was correct.

As the National Institutes of Health are concerned and biomedical research, we are very much concerned on this committee about it.

We believe this is where the money of the people should be invested, here and in other places in this bill. Dr. Wyngaarden, as you will recall, Mr. Neil and I were out at the ceremony of the Howard Hughes Medical Institute Program.

Do you remember one thing I said out there, I don't know whether you interpreted this correctly or not, when I said, some of the most unusual people testify before our committee.

I got to thinking after I left out there, what I meant by that is this: Able people, able people, and I am looking at several of them sitting around you. At NIH you have a great number of able people. When they come in to justify the budget request for their particular Institute, it is a pleasure to hear them.

Now, Dr. Wyngaarden, I hope this year that we can bring out a good bill. We are going to bring out one that you will like, Dr. Wyngaarden. You may like it a little more than you can tell some of those people out there. You can rest assured on that.

EMPHASIS ON RESEARCH PROJECT GRANTS

Let me ask you this now, Doctor. Do you agree with our committee's policy of placing primary emphasis on the support of investigator-initiated research project grants?

Dr. **Wyngaarden**. Yes, sir; I agree with the nice things you said about my colleagues, they are able. They are also unusual, so you are right on both counts.

Yes, sir; we agree with you in placing primary emphasis on the research project grant. Over the years, most of the creative and innovative research has resulted from the emphasis on the research project grant, which takes advantage of the creative opportunities generated by the people who are actually doing the research, to whom the new ideas occur as they develop in unforeseen events.

So many new ideas arise from the unanticipated result of research. Even a minor deviation may unlock an important new avenue of research. That occurs from the support of the individual investigator, and the exploitation of his or her ideas.

Mr. **Natcher**. Do you think we are right in specifying the number of projects to be supported in the Appropriations Act? How do you feel about that, Dr. Wyngaarden?

Dr. **Wyngaarden**. I think it is a helpful target to give us the view of the Committee as to where we should be.

We have a target expressed in the new stabilization policy that the Administration has proposed, which is a very good number. In 1970, we funded a total of about 10,000 research project grants. That number has gradually increased, and we crossed the 18,000 mark only two years ago. Therefore, the stabilization proposal does capture the award number close to its crest value.

I think that the specified number is one way of relaying the intention of the Congress. On the other hand, some Institute Directors feel that they have been compressed a bit with a precise number in supporting other mechanisms of research, but in general I agree with your statement.

NURTURING THE SCIENTIFIC ENTERPRISE

Mr. **Natcher**. Dr. Wyngaarden, in November of 1983, you delivered an address on nurturing the scientific enterprise at the annual meeting of the Association of American Medical Colleges, which was later printed, I believe, in the magazine Science.

If you were making that same speech today, would you make any changes in it?

Dr. **Wyngaarden**. In a situation of adequate and abundant resources, were we not facing the deficit, I would make very much the same statement, yes.

Mr. **Natcher**. During the overview hearings, I recall a question my friend Silvio Conte asked, and one of the questions I asked Secretary Baker, Secretary of the Treasury, and also Mr. Miller, the Director of OMB, when I said this to them:

You have a 16-percent increase in foreign aid and 13-percent increase in defense, and look at the reduction that you have in our bill, $4.451 billion below the 1986 level.

How do you justify it? Dr. Wyngaarden, we never did get a good answer.

Mr. Conte, I yield to you.

FUNDING LEVELS FOR BIOMEDICAL RESEARCH

Mr. **Conte**. Thank you, Mr. Chairman.

I would like to welcome Dr. Wyngaarden. There are many interesting advances to discuss with you, as well as some of the difficult fiscal issues that this budget presents us with.

I note this is the second year in a row in which the budget proposes to decrease funding for the National Institutes of Health from the previous year's level.

Are we spending too much money on biomedical research, Dr. Wyngaarden?

Dr. **Wyngaarden**. Sir, I wouldn't put it in quite those terms. The biomedical research enterprise is impacted by the constraints of the times, like others, and the Deficit Reduction Act and the Administration policies have together brought down the total budget authority for the NIH. We are constrained to live within those figures and support the very highest quality research we can, while protecting the most critical mechanisms.

Mr. **Conte**. Why is it, Doctor, that the President's budget proposes increases for research in the National Science Foundation, the Department of Energy, the Department of Defense and NASA, and proposed a decrease in the National Institutes of Health?

Dr. **Wyngaarden**. Sir, I wasn't in on the decisions concerning any of the other agencies, so I don't know what the reasoning was.

Mr. **Conte**. For the record, please provide the percent increase or decrease proposed for each of these agencies' research budgets.

Dr. **Wyngaarden**. Yes, sir.

[The information follows:]

RESEARCH AND DEVELOPMENT BUDGETS

The table below displays the estimated research and development budgets for the National Science Foundation, the Department of Energy, the Department of Defense, the National Aeronautics and Space Administration, and the National Institutes of Health at the 1986 revised estimate level, the 1987 request level, and the change from 1986 to 1987.

[Dollars in thousands]

	1986 Estimate	1987 Request	Change	Percent change
NSF	$1,294,060	$1,479,000	$184,940	14.3
DOE	655,928	773,400	117,472	17.9
DOD	33,736,392	41,929,900	8,193,508	24.3
NASA	2,611,461	3,003,100	390,639	15.0
NIH	4,894,900	4,671,500	−223,400	−4.6

RESEARCH PROJECT GRANTS

Mr. **Conte**. Now, in fiscal year 1985, after a lengthy battle with OMB, we provided for 6,200 new and competing grants. Is that how many you funded?

Dr. **Wyngaarden**. In fiscal year 1985, we funded 6,246 new and competing renewal research project grants.

Mr. **Conte**. In fiscal year 1986, we provided in the bill language for 6,100 new and competing grants. At the fiscal year 1986 enacted level, pre-sequester, would there have been sufficient funds to fully fund 6,100 new and competing grants?

Dr. **Wyngaarden**. We estimated that the downward negotiation would be up a percent or two, but very close to full funding.

Mr. CONTE. What effect does Gramm-Rudman-Hollings have on the funding of the mandated 6,100 grants?

Dr. WYNGAARDEN. The number would stay the same. The downward negotiation would increase to 9.3 percent for new and competing research project grants including the historical negotiations of 3 percent.

Mr. CONTE. If you were to get this sequester restored to you some time this summer, as a result of the Supreme Court decision on the case that I and 11 of my colleagues have brought to rule Gramm-Rudman-Hollings unconstitutional, would you be able to use these funds; and if so, for what purpose?

Dr. WYNGAARDEN. Yes, sir; we would then fund the programs as directed by the Congress according to the original appropriation.

RESCISSION PROPOSALS

Mr. CONTE. What is the purpose of the additional proposed rescission of $62.9 million? Is it to reduce the number of grants to what last year's budget proposed and what this subcommittee rejected in this bill signed by the President?

Dr. WYNGAARDEN. The rescission proposal would reduce the research project grants by nearly $54 million and 581 competing awards, AIDS research by $13.9 million, and the small and minority universities and colleges program by $9.1 million. These rescissions are in addition to the impact of the Deficit Reduction Act.

Mr. CONTE. Is that for Morehouse College?

Dr. WYNGAARDEN. You mean the later statement?

Mr. CONTE. The $9.1 reduction?

Dr. WYNGAARDEN. The proposed rescission would reduce that category to the 1985 program level, or $10 million overall. In the 1986 appropriation, the Congress increased it to $20 million. The rescission in this area was the last to be made after we had made numerous others to adjust the budget in response to the rescission needs.

Mr. CONTE. That rescission would provide for no new grants?

Dr. WYNGAARDEN. Approximately $5 million will be available for new grants. With respect to the total, the larger question you have asked, the rescission of dollars and numbers in research project grants is designed to reduce the commitment base such that the stabilization policy of 18,000 total awards in 1987 would permit a level of 5,140 new and competing awards. Were that reduction not made within the President's budget, we would be under 5,000 new awards next year.

PAYLINES AND AWARD RATES

Mr. CONTE. What would be the payline and percent of approved grants funded under the fiscal year 1987 budget request?

Dr. WYNGAARDEN. In 1987, the payline for NIH as a whole would be 160; paylines for the institutes would range from 140 to 190. The overall award rate is estimated at 27.4 percent.

Mr. CONTE. Has the NIH ever had an overall average award rate of less than 30 percent before?

Dr. WYNGAARDEN. Not within my memory. The award rate in 1985 was about 37 percent.

Mr. CONTE. 37?

Dr. WYNGAARDEN. Actually, it was 37.3 last year. I believe it is correct that we have not been under 30 percent.

RESEARCH CENTERS

Mr. CONTE. With regard to centers, what centers would make up the proposed 11 to be cut from the post-sequester level of 534 for fiscal year 1987?

And what two centers would not be funded as a result of Gramm-Rudman in fiscal year 1986?

Dr. WYNGAARDEN. The 11 research centers that would not be funded at the post-rescission level would consist of eight fewer specialized/comprehensive research centers, two fewer general clinical research centers, and one fewer biotechnology research center. The two research centers that would not be funded at the post-sequestration level would be in the specialized/comprehensive category.

OTHER SUPPORT MECHANISMS

Mr. CONTE. And with regard to other mechanisms, most of which I believe we level-funded in fiscal year 1986, what is the effect of the Gramm-Rudman-Hollings sequester and the fiscal year 1987 request on those mechanisms?

Dr. WYNGAARDEN. The sequestration applies a 4.3-percent reduction to all mechanisms in 1986. In 1987, reductions from the 1986 appropriation for the other mechanisms are the following: Other research grants, $72.5 million; research training, $20.5 million and 1,113 trainees; R&D contracts, $16.5 million; intramural research, $12.7 million; research management and support, $1.2 million; cancer control, $2.7 million; and construction, $8.6 million.

FUNDING AT 6,000 GRANT LEVEL

Mr. CONTE. With regard to fiscal year 1987, we have tried for the past two years to raise the level of new and competing from 5,000 to 6,000-plus. That has meant not only adding money to retain current services, but adding additional money to pay for 1,000 or so new grants.

Since the average grant is about three years, if we were going to hold to the idea of a 6,000-plus new and competing grant level, is fiscal year 1987 the last year we would have to add significant amounts of new money to reach that 6,000 level? Would we then have reached auto pilot, where current services would automatically be at approximately the 6,000-plus grant level?

Dr. WYNGAARDEN. If the number of competing awards is kept constant at any level with an average award length of about 3.3 or 3.4 years, we would reach a steady stage in the fourth year, in terms of total awards and competing awards.

The dollar cost would depend on the average cost increase. We are now attempting to get a better idea of what drives up the average cost. We also have an average cost target to be maintained by virtue of the Administration policy on rate of growth.

CURRENT SERVICES

Mr. CONTE. How much money, over and above the budget request, would we have to add to continue all activities in fiscal year 1987 at the fiscal year 1986 appropriations level of activity and to provide for 6,100 new and competing grants?

Dr. WYNGAARDEN. The current services budget for 1987, based on the 1986 appropriation and including the AIDS funding, is $5,870,750,000. That assumes the indirect cost savings of the new Administration proposal. Without the indirect cost savings, the figure would be $5,972,750,000.

Mr. CONTE. Roughly half a billion, Doctor?

Dr. WYNGAARDEN. Yes; 1987 current services would be about a half a billion over the appropriated 1986.

Mr. CONTE. A half a billion over appropriated 1986?

Dr. WYNGAARDEN. Not quite, but close. The actual amount would be $467.5 million.

Mr. CONTE. Thank you, Mr. Chairman.

Mr. NATCHER. Mr. Stokes?

FY 1986 RESCISSIONS

Mr. STOKES. Dr. Wyngaarden, I join with the chairman and Mr. Conte in welcoming you back before our subcommittee.

Doctor, how did you select those program areas that are targeted for rescissions?

Dr. WYNGAARDEN. Well, that is never easy. In the first instance, we projected the number of new awards and the average cost per award that was in line with Administration policy, and then, in order to maintain the primacy of the investigator-initiated research project grant category, other compromises had to be made.

As we went through the budget, with that in mind and with the rescission in mind, and the necessity of positioning ourselves in 1986 in such a way that the impact of 1987 would be distributed optimally, we came to a certain number of activities that we thought were of somewhat lower priority, although in themselves highly meritorious.

In areas in which there was unusual growth during this year, we felt that it was perhaps appropriate to hold those programs at the 1985 level, since that was the best we could do in almost all other programs.

Mr. STOKES. In the process, did you appeal any of these rescissions to OMB?

Dr. WYNGAARDEN. Yes, we did.

Mr. STOKES. Let me ask you about the small and minority universities program: the Academic Research Enhancement Awards and the Research Centers and Minority Institutions Awards.

My understanding is that there are many high-quality approved, but unfunded, applications for both programs. In fact, Mr. Conte asked you about Morehouse Medical School, which we understand is one of those that has an approved application, but has not yet been funded.

If this is correct, how do you justify rescinding $9.1 million for these initiatives?

Dr. **Wyngaarden**. NIH is proposing to rescind approximately $9.1 from this program, in addition to the mandated reduction of $900,000 due to the Deficit Reduction Act. The Congress, as you know, provided $20 million for this program in fiscal year 1986, an increase of $10 million over the fiscal year 1985 level, and over the 1986 request level.

Given the need to reduce the Federal expenditures because of the growing deficit, the Administration believed that such a significant add-on for a new program could perhaps be deferred, and that we might propose to stay with the initial appropriation level of $10 million during fiscal year 1987.

I want to assure you that the NIH is fully committed to solving the minority health problems, and the $10 million provides for continuation of a relatively solid program in this area of support.

Mr. **Stokes**. Well, I am somewhat constrained to question that, Dr. Wyngaarden. In reading your budget justifications, you state therein that the $9.1 million is to be rescinded because Congress added more money than was requested by the Administration.

Yet, when we look through the justifications, we find that there are many other programs within NIH to which Congress added more money than was requested by the Administration, but which are not proposed to be rescinded.

It would seem, if that is the criteria, that there is a double standard here.

Dr. **Wyngaarden**. I don't think so, Mr. Stokes. The level of NIH funding after the Deficit Reduction Act, and the rescission request overall, is rather close to the Administration request of last year, so one might say that the impact basically brings the proposed 1986 spending in line with the President's request for 1986.

I will grant you that we didn't apply that formula precisely throughout the entire program. We kept this one at the 1985 level. There are others that have been reduced even further—intramural NIH, for one.

RESEARCH OPPORTUNITIES FOR MINORITIES

Mr. **Stokes**. Doctor, are you satisfied that we are making enough progress in extending research and research training opportunities to minorities?

Dr. **Wyngaarden**. No, sir; I think we are always able to do more and to do better. I do think that the program we have proposed receives a proportionate amount within the fiscal realities of the day, but I would agree with the implication of your question that we can always do more.

BLACK COLLEGES

Mr. **Stokes**. Thank you. In 1984, NIH awarded $22.9 million in research grants to historically black colleges and universities. Excluding the new RCMI program, how much was actually awarded in 1985, and can you tell us what your goal is for 1986?

Dr. **Wyngaarden**. We will have to supply those figures for the record, Mr. Stokes.

[The information follows:]

Research Grants to Minority Institutions

Excluding awards made in the Research Centers in Minority Institutions Program, the NIH support in research grants to historically black institutions during 1985 was $26.2 million. It is estimated that the 1986 level of support will be essentially the same as 1985.

RESEARCH TRAINING

Mr. **Stokes**. All right, excluding the MARC program, six institutional training grants were made in 1984 to historically black colleges. Tell us how many were made in 1985, and your estimate for 1986?

Dr. **Wyngaarden**. Are you referring to the Minority Biomedical Support Grant Program?

Mr. **Stokes**. Institutional training grants to black colleges.

Dr. **Wyngaarden**. I don't think we have those figures with us at the moment.

Mr. **Stokes**. Supply those for the record.

[The information follows:]

Institutional Awards to Minority Institutions

Excluding awards made in the Minority Access to Research Careers Program, the NIH awarded 6 institutional training grants to historically black institutions during 1985. It is estimated that the same number of awards will be supported during 1986.

Mr. **Stokes**. Tell us what progress you are making in increasing the number of minority students supported through institutional training grants which are awarded to predominantly white colleges and universities?

Dr. **Wyngaarden**. Dr. Raub?

Dr. **Raub**. Recognizing that as an area of both special opportunity and special need, during the past year we identified this effort as an important initiative for our traditional institutional training grants.

We sent to all of the program directors an indication of our interest in stimulating their efforts to identify and recruit such students in the training programs.

We plan to follow that up with a specific revision in the guidelines for the preparation of applications and for the review of applications to do everything we can to ensure that every reasonable effort is taken at both the institutions' initiative and on our own review and award process to promote such review and follow through with those students.

Mr. **Natcher**. Mr. O'Brien?

NIH CLINICAL CENTER

Mr. **O'Brien**. You have a very heavy responsibility, and you do it well.

Stemming from personal experience, I had a bad back problem recently and I was entertained for a month in one of your Institutes at Bethesda. Years ago in real life, when I was practicing law, I did a lot of defense work, and I found myself rather critical of people who came in with back problems. If I had to do it over again, believe me I would be more sympathetic.

While I was a guest in your house, I managed to mosey around a little bit, and I saw that in almost every Institute I got in there were empty beds in the clinical end of your operation.

I also found that the equipment is superb. The degree of professional competence cannot be topped in my view. In terms of backgrounds and training skills, the people handling these particular assignments are also very highly competent.

Once you get beyond that level, it is very spartan. The room I had was "Illinois State Villa," accommodation-wise. That refers to the state penitentiary in my hometown.

The thing that troubles me is seeing the vacancy of beds. So I did a little inquiry, off-the-cuff questions of nurses and clinical specialists, doctors, and so on.

I found that most of these vacancies were simply there, not because we didn't have people lined up crying for a bed, but because we didn't have the personnel to staff them.

OCCUPANCY RATES AT THE CLINICAL CENTER

I follow on the heels of Mr. Conte's questioning. If we were able to staff, and I am not sure about my figures here, Doctor, but I had the feeling that there were about 15 beds in each clinic that didn't have staff to take care of them. Suppose you were able to staff those 15 beds. Where would we end up with respect to, I think, Mr. Conte's question, the figure of $450 million?

Where would we end up if we tried to compromise even at the level I am talking about?

Dr. **WYNGAARDEN**. Over the years, we have had varying occupancy rates in the Clinical Center. When the Clinical Center was built, it was designed to have about 500 beds overall. With some additional facilities such as intensive care units and other types, we have expanded beyond that, and could, with the plans laid out some years ago, end up with almost 600 beds, if those plans were put in force.

We usually have an occupancy rate of 65 to 70 percent of the 500 beds. Most teaching hospitals run in the 80- to 85-percent range; when they get above 90, the place is running a bit frantically. Our current rate is less than that level, and relates primarily to the 5 major work days per week.

Mr. **O'BRIEN**. Are we at 70 percent now, about?

Dr. **WYNGAARDEN**. Yes, we are usually very close to that during the 5 working days a week. Over the years, we have had various constraints that have kept us at about that level.

For many years, the dollar figure was perhaps the limiting factor and the FTE figure became——

Mr. **O'BRIEN**. Those are related. You are not going to get the personnel unless you get the dollars?

Dr. **WYNGAARDEN**. They are related, but somewhat different. The dollars might have been somewhat more available than the positions at the time——

Mr. **O'BRIEN**. That dollars are somewhat more available than the positions. You mean with respect to people competent to staff those positions, it isn't easy to find them. Isn't that due to the fact that people who work in those comparable positions in private enterprise make more?

Dr. WYNGAARDEN. That is true. During the present reduction of FTEs, we have given Dr. Decker an allocation of FTEs primarily to staff adequately the new cancer wards that were under renovation and have now opened some months ago. We have filled the majority of those positions, but still have 10 or 15 vacancies that we are not able to fill.

Mr. O'BRIEN. Suppose we were able to find equally competent staff to bring you from 70 percent to the 85 percent which I gather is a figure you consider sort of marginal within the area of not putting too much pressure?

Dr. WYNGAARDEN. It would put a lot of pressure on the support services.

Mr. O'BRIEN. Is 85 percent a reasonable figure to look at?

Dr. WYNGAARDEN. It would be less than that. We could do the vast majority of research; in fact, we are now. I was indicating that figure so we don't consider getting anywhere close to 100 percent; that would be counterproductive.

ADDITIONAL FUNDING FOR CLINICAL CENTER

Mr. O'BRIEN. I see. Let me ask it this way: Assuming that—and I am still looking at positions and dollars with the same set of glasses—and also with the main objective, getting the people in those beds who need that particular degree of care—if we were able to run, say, from 70 to 80 percent, how much additional money would you need over what you are asking for?

Dr. WYNGAARDEN. I don't know that we brought figures like that with us. We will be happy to provide for the record, sir.

Mr. O'BRIEN. I would appreciate if you would provide it for the record.

[The information follows:]

CLINICAL CENTER OCCUPANCY

To attain an occupancy rate of 80 percent in FY 1987 for the NIH Clinical Center would require approximately 116 FTE's and an estimated $8 to $10 million. There are a number of factors as to why it may not be desirable or practicable to operate the Clinical Center at full occupancy or even 80 percent. Examples include: the isolation of a patient in one bed of a semi-private room, a patient in a semi-private room is unable to have a roommate for various reasons (physical and mental problems that are disturbing to others), at the time the census is counted the patient is in another area such as the ICU, or the bed is in a special care room category reserved for patients with a special protocol or level of care requirement. In addition to these factors, the NIH would not want to attain 80 percent occupancy which could only be obtained at the expense of other programs.

Mr. O'BRIEN. I guess that will take care of me for the moment. I do want to compliment you, though, on the way you run your shop. It was first-rate.

Mr. NATCHER. Mr. Hoyer?

CHRONOLOGY OF THE BUDGET REQUEST

Mr. HOYER. Thank you very much.

Doctor, good to see you, sir. The cut for fiscal year 1987 was $17 million from our appropriated level in 1986, after sequestration on March 1, and the additional cut that has occurred.

How much did you ask for, Doctor?

Dr. WYNGAARDEN. In 1987?

Mr. HOYER. Yes, sir, the fiscal year 1987 request.

Dr. WYNGAARDEN. The NIH estimate to the Public Health Service was $6.415 billion. The PHS estimate to the Department was $6.093 billion, and the Department request to OMB was $5.907 billion.

Mr. HOYER. $5,907?

Dr. WYNGAARDEN. Yes; the actual figure was $5,907,355,000.

Mr. HOYER. As a result of the request of $4.9, approximately $1 billion less, or a 20-percent cut in your request, what will we be unable to do? That may be an inartful way to phrase it.

Dr. WYNGAARDEN. The $4.9 billion will support 5,104 competing research project grants, which is less.

Mr. HOYER. Would the $5.9 billion have supported 6,000 grants?

Dr. WYNGAARDEN. The main impact is in the research project grant category, and our request——

Mr. HOYER. Are you referring to page 15 of the document I have? You have got it in a different way.

Dr. WYNGAARDEN. Yes; it is in a different way. The present request would support 5,104 awards, not counting the AIDS awards, and the——

Mr. HOYER. $4.9? We can use $4.9 and $5.9, which is your request?

Dr. WYNGAARDEN. The Department's request to OMB was $5.9 billion, which would have supported 6,000 awards.

Mr. HOYER. That $850 million difference accounts for how much?

Dr. WYNGAARDEN. A principal difference is in the research project grant category, which is down to $2.8 billion, so that is about half of it.

Mr. HOYER. $500 million?

Dr. WYNGAARDEN. Yes; the actual number would be $575 million.

Mr. HOYER. What accounts for the other half-billion?

Dr. WYNGAARDEN. We have about $75 million less in research centers, Mr. Hoyer.

Mr. HOYER. How many fewer research centers?

Dr. WYNGAARDEN. The request would support 523, so it is a drop of 12 research centers at about $75 million less than the Department's request to OMB.

Mr. HOYER. I didn't count right. 535 versus 523?

Dr. WYNGAARDEN. Yes, dropping to $447 million in total costs. In other research——

Mr. HOYER. Doctor, would that mean that the number, the difference of $75 million, or is it also spread throughout the other centers, or just those centers, if I am following you, the 9 and 12, 21?

Dr. WYNGAARDEN. There are one or two others that have changed by a figure or two, but the bulk is in the specialized research centers.

Two general clinical research centers and one biotechnology center would not be funded.

Mr. HOYER. 12 centers, about $75 million?

Dr. WYNGAARDEN. Yes.

Mr. HOYER. That would just be for those centers? In other words, there would not be a commensurate, prorated reduction in the other centers?

Dr. WYNGAARDEN. There would be some adjustments. I believe the overall figure would be over 10 percent downward negotiation on the average for the remaining centers from the request level.

Mr. HOYER. Plus a 10 percent reduction across the board, approximately?

All right, sir. That gets us to $570 million, we have $430 million left?

Dr. WYNGAARDEN. There is a reduction of about $88 million in other research categories. The largest component of that is in the biomedical research support grant category at $67 million.

BENEFITS OF BIOMEDICAL RESEARCH

Mr. HOYER. How does that relate to your statement on page 4 of your prepared statement that we have saved $2.5 billion annually as a result of biomedical research, would that $90 million reduction relate to that area?

Dr. WYNGAARDEN. I was referring to some of the positive effects of health research.

Mr. HOYER. I understand. If you don't spend the dollars, you won't get the savings. Is that the kind of research you are talking about here?

Dr. WYNGAARDEN. Yes.

Mr. HOYER. You mention three of the 12 advances?

Dr. WYNGAARDEN. Yes.

Mr. HOYER. The committee would be very interested in the 12 advances to which you referred, and if you can ascribe a portion to each one of them.

Dr. WYNGAARDEN. We have the figures, yes.

Mr. HOYER. Those statistics are very dramatic and show how cost-effective the expenditures made in the Institute are. Excuse me, go ahead, sir.

[The following was provided for the record:]

RESEARCH ADVANCES

The 12 research advances to which I referred in my opening statement are the following:

Treatment of patent ductus syndrome—a heart defect of infants—with the drug indomethacin rather than through surgery. (Savings: $180 million)

Management of coronary artery disease through medical care and drugs rather than by surgery. (Savings: $500 million)

Prevention of stroke and stroke death by prescribed aspirin and standard hypertension control rather than through complicated neurosurgery. (Savings: $30 million)

Prevention of respiratory distress syndrome (RDS) in infants through steroid treatment before birth. (Savings: $295 million)

Diagnostic imaging techniques applied to brain tumors and other cancers. (Enormous impact; unable to quantitate.)

Wide local excision and radiation, rather than amputation, for treatment of soft tissue cancers. (Per person savings of about $70 thousand; not a great impact in the aggregate, as this type of cancer is relatively rare.)

Laser treatment for three eye disorders—angle-closure glaucoma, diabetic retinopathy, and aging-related maculopathy. [Note: entry comprises 3 of the 12 research advances.] (Savings: $154 million)

Percutaneous transluminal coronary angioplasty rather than coronary artery bypass graft procedures for single vessel atherosclerosis. (Savings: $156 million)

Accurate assessment of fetal maturity to prevent prematurity associated with cesarean delivery. (Savings: $325 million)

Development of specific criteria on which to base decisions on whether surgery is indicated in recurrent throat infections, thus decreasing unnecessary tonsillectomies. (Savings: $818 million)

BUDGET REDUCTIONS

Dr. **WYNGAARDEN**. We have a reduction of $22 million from the Department's request to OMB in training, including a reduction from 10,152 trainees to 9,258. Contracts are reduced about $118 million.

Mr. **HOYER**. What does contracts being reduced mean, sir?

Dr. **WYNGAARDEN**. We do a number of things by contract: some are procurement, and some are activities that augment research, such as the acquisition of certain chemicals, drugs, biologicals with which research is being done.

Clinical trials are often done by contract, so we would be funding far fewer new clinical trials in 1987.

Mr. **HOYER**. I understand the AIDS reduction is a significant portion of that as well?

Dr. **WYNGAARDEN**. The request for AIDS is currently in the Assistant Secretary's budget. After the effects of the deficit reduction and rescission, we have about $120 million in AIDS research at the NIH for 1986. The request for 1987 is for $143 million in AIDS research.

Mr. **HOYER**. How much did you request?

Dr. **WYNGAARDEN**. That is what we requested in 1987.

Mr. **HOYER**. That would not be part of the billion dollar reduction?

Dr. **WYNGAARDEN**. No, sir.

Mr. **HOYER**. I think my time is up.

NEW STABILIZATION POLICY

Mr. **NATCHER**. Dr. Wyngaarden, we are sometimes confused as to the Administration's intentions with regard to biomedical research. On the one hand, we are told that the 1987 budget "will permit a continued, long-term and sustainable Federal commitment to maintain NIH's unparalleled record of excellence in supporting biomedical research."

This statement appears on page 146 of the OMB document entitled "Major Policy Initiatives." On the other hand, we find that the budget proposes to reduce competing projects from 6,219 in 1985 to 5,492 in 1986 and 5,104 in 1987.

Can you clarify this apparent contradiction between words and deeds? What do we have here, Dr. Wyngaarden? What would you like to say about it?

Dr. **WYNGAARDEN**. The reduction is attributable, Mr. Natcher, to several factors. The first of these is, of course, the Federal deficit and the need to bring that under control, and the participation of the NIH in that effort.

In addition, these reductions reflect the new stabilization policy, which puts the focus on the total number of active awards, rather than the number of new starts. The 18,000 limit proposed by the Administration results in a variable number of new and competing awards each year.

Essentially, the 18,000 minus the continuation obligations generates the figure for new and competing awards; 5,140 with the AIDS projects is the lowest point in this adjustment for the next several years.

The figure averages about 5,500 new and competing research project grants with that new approach, between now and 1993, and the 1992 figure would be the only one that is under the 5,000 mark. All the rest would be above that, averaging about 5,500. These reductions reflect a desire and a need to bring the commitment base into conformity with the fiscal requirements for planning over the next several years.

THE FOCUS OF NIH

Mr. **NATCHER**. Dr. Wyngaarden, the President's top science advisor, who recently left the White House to form a consultant firm, said in a recent interview, and I quote:

"What I am afraid of is that NIH is not focusing on the real questions. In the biological sciences, we should be looking at neurobiology, to take one field out of dozens, and ask whether we are capturing the potential there and whether we are drawing the young people we should be.

"NIH has been managed primarily by Congress, not by the Executive Branch. I would be more comfortable if we focused on excellence."

Dr. Wyngaarden, explain to us why the President's science advisor says, number one, NIH is being managed by Congress. Number two, NIH is not focusing on the real questions. And three, Doctor, NIH should focus on excellence.

Dr. **WYNGAARDEN**. I think we are focusing on excellence, and I think the record speaks for itself on that. We are supporting the best qualified scientists, the highest priority research projects as judged by the scientists themselves through the peer review system. The neurosciences constitute one of my highest priorities; in the construction of the 1986 budget which your committee recommended, I had singled out the three major areas through which we support neurological science for larger than average increases: the National Institute of Neurological and Communicative Disorders and Stroke, the National Eye Institute, and the Aging Institute.

In fact, the increases approached 10 percent in the budget request last year, reflecting my sense also that there are marvelous and important opportunities in neurosciences at present.

Those two points are easily defended. With respect to the final point, that Congress is managing the NIH, I think this statement reflects the fact that, for a number of years, the Congress has tended to increase the Administration request. That situation dates back 20 years, as you know much better than I, and I suspect that Dr. Keyworth is suggesting, with that strategy or practice, go a certain number of determinations of priorities.

But I emphasize that Dr. Keyworth is speaking for himself. He is not speaking for me.

Mr. **NATCHER**. Dr. Wyngaarden, that is a good answer.

INCREASES IN FEDERAL R&D

Now, Doctor, we look at page K-14 of the special analysis of research and development in the President's 1987 budget document, and we find that total Federal obligations for the conduct of research and development are projected to increase from $49.5 billion in 1985 to $52 billion in 1986, and to $60 billion in 1987.

That is an increase of over $10 billion. NIH, however, is projected to decrease over the same 3-year period. What comment do you have to this, Doctor?

Dr. WYNGAARDEN. There are policies set by the Administration that clearly have given a high priority to those areas of research that contribute directly to national defense, and the NIH, although maintained at an effective level, is not being proposed for the kind of increase envisioned in other areas.

AVERAGE COST INCREASES

Mr. NATCHER. In our conference report on the 1986 Appropriations Act, we expressed concern about the continual rise in the cost of the average NIH research grant. Are you taking steps to address this problem, Doctor?

Dr. WYNGAARDEN. Yes, sir, we are. The first thing we have done is to conduct a much more careful analysis than ever before of the factors that have operated to increase the average cost of grants.

The average cost applies not just to the RO-1, but to eight different types of grants in the overall category, such as the very large program project grants as well as the new SBIRs. The change in the mix of these grants influences the average costs.

The average cost of the RO-1, the traditional grant, is about $138,000. The average SBIR, phase two, is $216,000, so there is a substantial impact on the average from the change of mix, but the change of mix is not the most important factor that pushes the average cost up.

The growth in the personnel category has exceeded the growth rate of equipment and of supplies, and beyond that, the indirect costs are 50 percent greater per year than the growth of the other components of the average costs.

Within the direct cost component, we find that the escalation from one year to the next of a multiyear award is a factor, but not the largest factor. The largest factor is the renewal application, which generates a jump step in average cost.

For example, we award a young and relatively untried investigator an award for 3 or 4 years at a fairly modest sum. If that investigator does well, when he or she applies for a competing renewal of that award, the average increase is likely to be 30 percent. This increase reflects the fact that the person is moving from an introductory phase of research into a program that in his or her judgment warrants some expansion or growth. That is a perfectly natural aspiration.

The sum total of all those factors has resulted in an average rate of increase over the last 5 years of around 10 percent per year.

CAP ON INDIRECT COSTS

Mr. **Natcher**. Doctor, as you know, the Federal Register for February 12, 1986, includes a proposed revision to OMB Circular A-21, which would limit the reimbursement rate for university administrative overhead costs to 26 percent on April 1, 1986, and to 20 percent by April 1, 1987.

Did you recommend this change?

Dr. **Wyngaarden**. Some time ago we recommended a change to the Department that was a little different.

The study of indirect costs by the Inspector General recommended the capping of certain components of the administrative expense categories, but not all. We recommended that all these be collected into one category to preclude the possibility of shifting costs from one category to another. We also recommended that indirect costs be capped with some recognition given to the historic average of those costs in specific institutions.

The NIH proposal, when reviewed at other levels, was modified somewhat, so that the proposal as it now exists would reduce the category of all administrative costs, Departmental administration, research administration, general administration, and the cost of administering certain student programs.

Those costs are to be capped at 20 percent of the direct cost figure. The historic figure is 26 percent. The proposed reduction to 20 percent is a compromise. There had been a proposal to reduce one category from 15 to 7 percent, which would have been an 8-percent cut—slightly larger than the currently projected 6-percent average reduction.

Mr. Williams may want to speak to that, also.

Mr. **Williams**. The Department in general has supported moving in this direction. The proposal published on February 12 is still a proposal, requesting public comment. One of the items that the Department will be commenting on is that the effective date in the current proposal is later than we would like it to be. Our budget assumes some savings in 1987, with implementation in October of 1986.

So, one of the comments we will be making is that the effective date ought to be earlier. We are pleased that the Circular change will apply to all programs, and it doesn't single out this Department. It affects Government-wide operation.

Mr. **Natcher**. Mr. Conte, I yield to you.

INDIRECT COST REIMBURSEMENT

Mr. **Conte**. Should research institutions be able to recover the indirect costs of doing research?

Dr. **Wyngaarden**. Yes, sir; I think so.

Mr. **Conte**. What, in your opinion, is wrong with the current method of computing indirect cost reimbursement?

Dr. **Wyngaarden**. The current category includes seven subcategories; some are rather easily audited, such as space and energy costs, while others are more difficult to audit, primarily administrative costs, which are more complicated. The Inspector General found a number of instances in which the administrative costs had been increased in a way that was very difficult to justify.

The records that would permit an audit of some categories were sometimes not available. There were a number of examples of the unavailability or incompleteness of records.

In addition, major expenses are generated by the requirements of recordkeeping within the institutions, such as time and effort reports.

The proposal, which would reduce the indirect cost allowance, clearly reduces the flexible dollars going to the institutions, but it also reduces some of the requirements currently laid on the institutions, so there are some savings to be realized.

I don't think that they balance out, but institutions are nevertheless going to recover some of those costs by reduced requirements for recordkeeping.

Mr. CONTE. In the OMB proposal, the 26-percent reimbursement rate, which would be in effect for a year starting April 1st, I believe, is justified as the average indirect cost rate. That rate would then go down to 20 percent thereafter.

What is the justification or the rationale for this 20 percent rate?

Dr. WYNGAARDEN. The 20-percent rate represents a compromise. The Inspector General's report proposed reducing departmental administration from 15 percent of modified direct costs to 7 percent. In the judgment of the Inspector General, the large part of the departmental administration costs provided little or no benefits to research, and was the fastest growing component of the indirect cost portfolio as well as the least well-documented. Further, it is the area in which a reduction could be coupled with elimination of certain reporting requirements, and therefore would result in some savings to the institution.

Mr. CONTE. Would university research done for the Defense Department be subject to this new policy?

Mr. WILLIAMS. I believe they would.

Mr. CONTE. And do you know if the Defense Department supports or opposes this new policy?

Mr. WILLIAMS. I couldn't comment on that. We have not communicated directly with them.

Mr. CONTE. I understand they oppose it. I think you know that.

EFFECT OF INDIRECT COST POLICY

Would this new policy affect all institutions proportionately, or would it have a harsher effect on some institutions over others?

Dr. WYNGAARDEN. There are institutions that are well above the percentage cap, and they would be affected. Those that are under would not be affected.

Mr. CONTE. Do you think 30 days is a reasonable comment period?

Dr. WYNGAARDEN. That may be a little short. There is, of course, a long history of these discussions, Mr. Conte.

One of the first issues I confronted four years ago was the indirect cost issue, so it has been under active discussion for at least that period, to my knowledge, and probably another year to Dr. Malone's and Dr. Raub's knowledge.

AIDS FUNDING

Mr. **Conte**. In the fiscal year 1986 appropriations bill, we basically doubled the request for AIDS research, and put the additional $70 million into your office to spend in the best manner you saw fit.

How are you planning to expend this pool of money?

Dr. **Wyngaarden**. Yes, sir; we have allocated about $50 million of the available funds in accordance with the recommendations of the NIH AIDS Executive Committee.

We are holding about $3 million in reserve to retain some flexibility to deal with emerging problems or major opportunities as they occur.

Approximately $16.9 million of the original $70 million is marked for reduction, either through the Deficit Reduction Act or the rescission request.

Mr. **Conte**. Do you have enough funding to accomplish all the productive research on AIDS that you believe can be undertaken?

Dr. **Wyngaarden**. The generous increase of the Congress last year, which essentially doubled our budget, will permit us to fund the vast majority of the high-quality research, yes, sir.

Mr. **Conte**. In your report, you list additional approved projects that will not be funded under the fiscal year 1986 revised budget. We got your report this morning.

Assuming that the rescission request of $13.9 million is not approved, will you then have the funds to undertake these approved projects?

Dr. **Wyngaarden**. Yes, sir, we would.

Mr. **Conte**. You better go back and start planning on that, then.

AIDS DRUG AND VACCINE DEVELOPMENT

Tell us what promising drugs and/or vaccines are under study, and give us a sense of the time frame you are looking at for the development of these possibilities.

Dr. **Wyngaarden**. With your permission, I would like to call on Dr. Fauci, our AIDS Coordinator.

Dr. **Fauci**. Since we spoke before this committee last year, Mr. Conte, at least five drugs have gone through a process of being evaluated by the NIAID/NCI Drug Selection Committee. This group determines which drugs that have been submitted for possible testing should go on for further clinical evaluation by our AIDS Treatment Evaluation Units, which will be operational this coming spring or early summer. The five drugs I referred to are Ribavirin, Foscarnet, HPA-23, Suramin, and Azidothymidine.

Each of these drugs has been shown in the test tube to have activity against the AIDS retrovirus, and all have been tested in small phase I studies throughout the country, including the National Institutes of Health Clinical Center.

None of them is a cure. Our strategy will be to use them either alone or in combination with other drugs that might build up the immune system, so we do have a number of drugs that indeed are being tested.

In addition, our strategy includes being able to screen a large number of other drugs and put them into the hopper, as it were, to test them at the same time that we are testing, in later phases, the five that I just mentioned. So we have an active mechanism to test drugs.

With regard to vaccines, now that the AIDS retrovirus has been isolated and cloned, which means we have it in a totally purified form, the genetic makeup of that virus has been elucidated very, very clearly. This has allowed us to pinpoint what part of the virus would be most susceptible to being used as a focus for a candidate vaccine; namely, what part of the virus the body makes its immune response against, and that is the envelope of the virus.

Scientists in a number of institutions, with much of the basic work being done by the Cancer Institute at the present time, have isolated and purified the viral envelope and already injected it into monkeys. It has been shown, in fact, to elicit a neutralizing antibody, which means that the antibody in the test tube is able to block the growth of the virus.

Now that this has been shown, the next phase of the study underway involves challenging an immunized chimpanzee with the virus to determine if prior immunization with this envelope protein will be able to protect the chimp from challenge with the virus.

If this proves successful, then we can go on to the next phases. Thus, a lot of progress has been made, both in drug development and testing, as well as in vaccine development. Hopefully, testing will begin in the foreseeable future.

Mr. **Conte**. That sounds most encouraging.

Thank you, Mr. Chairman.

Mr. **Natcher**. Mr. Stokes?

BLACK TASK FORCE

Mr. **Stokes**. This past October, former Secretary Heckler released a rather long-awaited task force report on black and minority health. In fact, Dr. Malone, who is here with you, spearheaded that effort and did an extraordinary job, I think, on one of the finest reports we have ever read.

Were there recommendations in that report for activities NIH should be undertaking to improve minority health status?

Dr. **Wyngaarden**. I will turn this over to Dr. Malone.

Dr. **Malone**. Thank you very much for your comments on the report. You saw the executive summary, and there are seven additional volumes that are in press now, which will be released to amplify those basic results.

The recommendations indeed do impact on most of the Institutes at NIH, and there are a great many recommendations that have to do with things that can be done by the private sector.

In an informal way, I would say that most of the Institutes have paid very close attention to the recommendations, and are including them in their annual plans.

I think there will be a more formal mechanism of this coordination, since the Secretary, before her departure, established an Office of Minority Health. A Director has been appointed, Dr. Herbert Nickens, and he is in the process of developing an overall plan to discuss the recommendations with all the agencies in the Department and elicit from the various agencies their plans to implement recommendations that apply to them.

I have informally surveilled the various Institutes at NIH to get a sense of what is going on, and have found that a great deal of NIH already is responding to the recommendations of the task force report. I can provide that, or the Institute Directors may want to speak to that directly, but there is already a great deal of response to the recommendations of the task force report.

Mr. STOKES. I would appreciate, Dr. Malone, if you would provide for the record the follow-up activities going on relative to that report.

[The information follows:]

DHHS - National Institutes of Health

INITIATIVES SUPPORTING RECOMMENDATIONS OF SECRETARY'S TASK FORCE ON BLACK AND MINORITY HEALTH

Listed below, by Institute, are examples of initiatives supporting the recommendations of the Secretary's Task Force on Black and Minority Health:

NCI

o Issued three solicitations for contract research that will develop, test, and implement community approaches to prevent and control cancer in black communities. The five-year projects include research involving primary cancer prevention in blacks, avoidable mortality from cancer in blacks, analytic support and quality control.

o Facilitating the development of a "Network for Cancer Control Research In Black Populations." This network will foster research capabilities and form a national critical mass of investigators interested in conducting research to decrease cancer in blacks. The network involved the four black medical schools and investigators at other medical institutions and schools of public health.

o Will fund two studies on smoking cessation within black populations. The studies will involve 2,400 adult smokers.

o Fund three projects aimed at smoking cessation in the Hispanic community.The first is a community intervention program to reduce smoking in low-income Hispanic populations in Texas. More than 70,000 persons will be directly affected by the program, and 2.5 million will be exposed to the media campaign. The second, in the San Francisco area, involves 1,700 smokers. The third, in New York, will test the effectiveness of a classroom smoking prevention program in 30 junior high and intermediate schools.

o A consortium of black medical schools has successfully competed for a cancer center planning grant. The grant will help the consortium design a future minority consortium cancer center, vitally important to reduce cancer mortality in blacks.

o Studying differentials in survival rates between black and white patients for cancers of the breast, corpus uteri, colon, and prostate. The study is expected to provide information needed to improve survival differences pointed up in the Secretary's Task Force Report.

o Begin a major effort to reach Hispanics with cancer-related health information. Establish a Hispanic Outreach Task Force to recommend priorities and review materials produced in the Spanish language. The Task Force will recommend the most effective channels for distributing Hispanic materials and will help enlist the efforts of Hispanic organizations in disseminating the materials.

NHLBI

- o Issued a solicitation for contract research entitled "Health Care Seeking Behavior Among Blacks for Acute Symptoms of Coronary Heart Disease (CHD)." The primary objective of this proposal is to identify current concepts, beliefs, and behavior regarding symptoms of acute CHD among blacks.

- o Planned a workshop on Health Care Behavior in Hispanics regarding Cardiovascular Disease (CVD) and Risk Factors. There is a need for more information on the prevalance and relative importance of major CVD risk factors in Hispanics.

- o Planned a workshop on Diabetes Mellitus (non-insulin dependent) and its impact on the cardiovascular health of Blacks, Hispanics, American Indians and Japanese. The primary objective is to focus on this major health problem for these four large minority groups since the prevalence and mortality rates are higher for them.

- o Planned a project research to measure urinary sodium levels since hypertension is a major problem in blacks.

- o Issued a solicitation for a research project to study the biological and behavioral factors in smoking relapse. The Task Force was asked to include studies on the potentially different responses of minority populations to smoking cessation.

- o Issued a solicitation for a research grant to study coronary heart disease in the elderly. Four population based cohorts, ages 65-79 years, will be enrolled in a prospective 6-year study. One cohort will be minority.

- o Two research initiatives were significantly modified or their planning process accelerated as a response to the early work done by the Task Force on Subcommittee on Cardiovascular and Cerebrovascular Health. 1) The National Growth and Health Study (formally titled Obesity in Young Black and White Females) is a study of the relationship of obesity, especially in black females during and after adolescence, to lipoproteins and other factors. This is a long-term, collaborative study which includes both black and white female children, ages 9-10 at entry, to study obesity. 2) The second program that should provide important information is the Atherosclerosis Risk in Communities study. This is a long-term program to measure associations of established and suspected CHD risk factors with both atherosclerosis and new CHD event in men and women from four diverse communities. One cohort will be entirely black and a second cohort about 20% black.

- o Sarcoidosis is a lung disease with a high incidence among minority populations compared to white populations in the U.S. that is intrinsic to race or ethnicity. The Institute will issue a Contract Solicitation for use of molecular biology technology in an attempt to identify the etiology of sarcoidosis. This could ultimately lead to a less invasive method of diagnosis of this disease.

NHLBI (cont'd)

o Issued a program announcement to study nutrition in sickle cell anemia. The goal of this study will be to encourage research on nutritional assessment of children with sickle cell disease and to strengthen the data base on the role of nutrition on the clinical spectrum of sickle cell disease. Small studies have suggested that caloric supplementation improves the growth parameters in young children with sickle cell disease and reduces the incidence of sickle cell crises.

o Continuing the National High Blood Pressure Education Program. Professional, public, and patient education activities include: dissemination of program strategy programs for detection, treatment, and control of hypertension dissemination of health information and educational materials; technical support to federal, state, and local programs, working with federal and outside intermediary groups in the development and implementation of these activities; acquisition and/or analysis of data relevant to minority populations.

o High Blood Pressure Mass Media campaign. Public education via television, radio, and print public service ads targeted in part to minority audiences and relevant intermediary groups--developed with input from variety of minority representatives.

o National Cholesterol Education Program and National Smoking Education Program. Professional and patient education activities include: outreach activities, educational materials, health information, data acquisition; working with minority intermediaries; providing technical support.

o Minority Forum. Professional education and cooperation with intermediary groups in the public and private sector in the planning and implementation of this June 1986 conference.

NIDR

o Initiated educational activities to address the problem of dental health in low-income minority groups. Generally, among some of these groups, the caries rate is double that of the national average, the extraction rate is ten times as high, and baby bottle tooth decay is as high as 70 percent.

o Developed two posters--one in English and one in Spanish on how to prevent baby-bottle tooth decay.

o Received clearance to produce 5 posters on the use of fluorides and sealants. These posters will be in English and Spanish.

o Initiated efforts to provide health messages to minority groups, via local newspapers, radio and T.V.

NIDR (cont'd)

- Developed a project that will provide intramural training opportunities for minority dentists; will co-sponsor a three-year training program for students from MARC-supported and MARC-eligible institutions.

- In 1985, instituted two initiatives approved by the National Advisory Dental Research Council: 1) an already-funded grantee could apply for supplemental funds to support an approved research project by a minority investigator, and 2) start-up funds for research projects when minority investigators who have received NIDR training support return to their minority institutions.

- Analyzed data from the National Dental Caries Prevalence Study of 1979-80, differences in dental status between black and white children. A follow-up survey is planned for FY 1987.

- Differences by race in adult oral health will be examined and compared to similar data collected in an earlier National Center for Health Statistics (NCHS) study. NIDR staff have been working with the NCHS staff to process data from an earlier study comparing Southwest Hispanic data with information from the National Caries Study.

- An initiative is under way which will address the special problems that exist among some groups of native Americans where the incidence of diabetes is high and is associated with high prevalence and severity of periodontal diseases.

NICHD

- Designed and initiated a study on infant mortality/low birth weight (LBW), Better Babies project in Washington, D.C., to determine if outreach combined with intervention can reduce the incidence of LBW (15%) in an area of the city where it exceeds the national rate (7%).

- Will fund 6-8 applications which would look at the the role of the brainstem and other central nervous system centers in the control of vital functions as related to Sudden Infant Death Syndrome. This syndrome occurs more frequently in male infants, low birth-weight infants, black infants, infants of teenage mothers, and infants of mothers who smoked during pregnancy.

- Will fund studies on Teen Contraceptive Behavior. Out-of-wedlock births have been steadily increasing nationwide. According to data from 1983, the ratio for live births per 1,000 was 86.4 for minorities versus the national average of 29.7.

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NIA

- Issued a solicitation for research grants to study "Mechanisms Responsible for Age-Related Increase in Blood Pressure" which will look at the underlying causes for the increase in blood pressure with age and specifically calls attention to the nonwhite population. A special effort was made to include minority investigators in the mailing of the solicitation.

- Planned a workshop on Black Aging which is intended to promote increased research on health issues related to aging of black populations.

- Initiated plans to establish an exploratory research grant program for studies on aging of minorities. The research is aimed at increasing our knowledge of aging in minority populations and should ultimately lead to improved health care and quality of life for minority elderly.

NIAID

- Awarded two contracts to improve tissue typing of histocompatibility antigens from blacks, with the goal of improving the success rate of organ transplantation in black Americans.

- Awarded a contract for a clinical trial in Alaskan infants (Eskimos, Indians, and Aluets) of Haemophilus influenzae type b vaccine for the prevention of meningitis.

- Scheduled a community outreach conference on AIDS, targeted to the black community for 1986.

RESPONSE BY EXTERNAL COMMUNITY

Dr. **Malone**. If I could make one other statement, I would like to indicate that there is also a very large movement going on in response to the task force report in the external community.

For example, back in December, we conducted a one-day seminar on the task force report with all the health workers in the State of Ohio—some 300 people, including State representatives and representatives from the Governors' office. As a result of that effort, Ohio has established its own task force, which will implement for the State the recommendations as they see it.

The same thing has been done in the State of Indiana under Woody Myers, and similar activities are occurring for the States of California, Maryland, and Georgia. In addition, many professional societies are centering the national means around the task force report.

Thus there is a very fine opportunity for activities ongoing both within and without the Federal Government. I am very gratified by that movement, and I think Dr. Nickens has a good opportunity to follow up on the report.

Mr. **Stokes**. It has been my own experience in my travels around the country that the report has generated a great deal of interest and concern and response, and as you say, externally.

You mentioned the other volumes. When can we anticipate that the other volumes will be delivered?

Dr. **Malone**. Four volumes were released just 2 weeks ago: infant mortality; diabetes; homicide, suicide, and unintentional injuries; and cardiovascular disease. It is my prediction that the other three volumes will be forthcoming within the next month. They are being edited now.

Mr. **Stokes**. Very good.

EMPLOYMENT DISCRIMINATION

Dr. Wyngaarden, last year we had a great deal of discussion here about charges of discrimination in employment brought by employees at NIH. Subsequent to that, Congressman Hoyer, who is here, and I asked that the GAO evaluate affirmative action policies at NIH. That report has now been completed.

I understand NIH commented on the draft report and that a final report has now been forwarded to you. I have several questions to pose to you, but first let me have you insert in the record for us a comprehensive response to problems identified by GAO.

Do that in the record for us.

[The information follows:]

Response to GAO Report

The NIH was found not to be in full compliance of four of eight Federal requirements for affirmative action. These four requirements are below, as are the corrective actions that will be undertaken to fully meet affirmative action requirements:

Establish numerical hiring goals:

The Director, NIH, has appointed a committee to develop methodology for establishing meaningful goals that will meet the EEOC requirements. Once goals are established, this committee will develop a mechanism for implementation of these goals within the NIH. To augment the committee's actions, the NIH Division of Equal Opportunity (DEO) has already investigated the use of automated systems for the calculation of goals and manipulation of data for meeting affirmative action requirements and has proceeded with preparing the documentation required to purchase the necessary computer hardware and software packages.

Develop and implement minority and female recruitment plans in those organizational components that do not have them:

The Director, NIH, plans to direct the five components that do not have minority and female recruitment plans to prepare and submit them to the DEO. It should be noted that the Office of the Director (OD) Personnel Office has already begun the development of an Affirmative Action Program (AAP/Federal Equal Opportunity Recruitment Program (FEORP) plan for the Office of the Director and the Office of Research Services. The National Library of Medicine has also begun the development of a FEORP plan for minorities and women.

Identify and eliminate employment barriers for minorities:

NIH has conducted barrier analyses in accordance with the Public Health Service guidance on AAP/FEORP. Analyses of four series have been completed at NIH. It is anticipated that analyses of the remaining target series will be completed before the end of FY 1986. Should any barriers to equal employment opportunities be found, NIH will take appropriate action to correct the situation.

It should also be noted that NIH participated in the development of the methodology for a PHS-wide study on barriers to the employment of Hispanics and native Americans, conducted a barrier analysis in NIH component organizations, and participated in analyzing data and writing the PHS final report issued in September 1984. Since that time, NIH has implemented several of the recommendations contained in the PHS report.

Collect data on the race, ethnic origin and gender of job applicants to monitor and evaluate the effectiveness of affirmative action efforts:

The NIH discontinued collecting data on the race, ethnic origin, and gender of job applicants based on instructions received from the U.S. Office of Personnel Management (OPM). The OPM issued a letter in December 1983 indicating that these data should no longer be collected because the Office of Management and Budget authorization to use the OPM Form 1386, Background Survey Questionnaire, had expired. As pointed out in the GAO report, the NIH, as well as other Federal agencies, is required by Equal Employment Opportunity Commission (EEOC) regulations to collect data on applicants, but is caught in a bind between EEOC and OPM, who allowed OPM Form 1386 to expire without seeking its reauthorization.

The NIH, in April 1984, sought guidance on this issue from the Department of Health and Human Services, which in turn sought guidance from the U.S. Office of Personnel Management. The DHHS was unable to resolve this matter with OPM. Until this issue is resolved, NIH will be unable to meet this affirmative action requirement. The inability to collect these data also impacts on the "adequacy" of barrier analyses being conducted by the NIH.

GAO INVESTIGATIVE REPORT

Mr. STOKES. In general, GAO found that NIH increased the overall representation of minorities in the work force from 24 percent in 1979 to 27 percent in 1984, but that minorities and women remain underrepresented in 63 of 108 race, ethnic origin, gender, occupation and grade level categories.

GAO concluded that increased effort, strong commitment and active support by NIH top management are needed to bring its affirmative action plan into compliance, and to improve the representation of minorities and women.

Can you comment on these figures for us?

Dr. WYNGAARDEN. We are aware, of course, that the distribution of minorities throughout the various position grades at the NIH is not symmetrical and not proportionate.

There has been improvement in the number of minorities at the GS-13 and above levels in the past years, from 82 in 1979 to 119 in 1985.

That is nearly a 50-percent increase in 6 years, so we are making some progress. I am not satisfied with it, but it is gradually improving.

We are paying a great deal of attention to the GAO recommendations. A little over a year ago, we reorganized our Office of Equal Opportunity, and the Director has been working on many of these opportunities to improve the showing reflected in those figures.

Mr. STOKES. One particularly striking finding of the GAO, when it looked at the underrepresentation of minorities in specific categories, is that minorities are severely underrepresented in Senior Executive Service positions at NIH.

The number of blacks in SES positions has increased from only three in 1979 to only four in 1984, and the number of Asians in SES positions has increased from two in 1979 to three in 1984.

In total, 96 percent of all the SES Positions at NIH are held by whites, primarily white males, in an agency with 27 percent minorities overall.

When one looks at your agency and finds minorities and women overrepresented as clerk typists and technicians and are severely underrepresented at the upper levels of the agency, would you agree that this situation can contribute to a perception that you are not committed to recruiting and promoting qualified minorities?

Dr. WYNGAARDEN. First, I think my figures show a larger increase, in the Executive Service, from three in 1979 to six in 1985. In the other levels, we have a 50-percent increase from 1979 to 1985, so we are making progress.

There is no question that minorities and women are underrepresented at these more senior managerial positions. That reflects no lack of interest on my part in identifying minorities and women for those positions.

We have a sociological phenomenon that goes far beyond the intentions of NIH, reflecting the fact that the increase in the number of minorities and women in certain career tracks is a rather recent event. The time involved in formal or postdoctoral training, administrative experience, and the breadth and diversity of activities that make one eligible for some of these senior positions takes a number of years.

I expect we will continue to see an improvement in the figures that you have given, and that I have given, as the number of minorities and women entering professional and medical schools increases, and as their subsequent experience brings them, say, 20 years later to the point where they can compete for these more senior positions.

We certainly fully intend to exercise our stewardship in seeing that this takes place.

Mr. STOKES. Thank you, Mr. Chairman.

Mr. NATCHER. Mr. O'Brien?

OCCUPANCY RATE AT THE CLINICAL CENTER

Mr. O'BRIEN. On this committee, we tend to think in dollars. That is what we are supposed to be doing. I get a little bit lost in the business of personnel ceilings, OMB limitations, things of that sort.

I would really like to find out if we could manage to make something of an end run around OMB constraints, legitimately.

What I am trying to find out from you is what would we need to come up with here to fill the beds, to suit your aspirations and mine. Assuming that we would be able to deal with OMB in an appropriate fashion?

Dr. **Wyngaarden**. I think the premise on which your question is based makes it difficult for me to respond. My role is to defend the Administration decisions, and to assure you that within the resources made available to us, both in dollars and positions, that we are able to approach our highest priority research activities, including those in the clinical area, and I am prepared to do that.

Mr. **O'Brien**. I understand, and I don't quarrel with you for that. I have no problem with that part of your problem. It is our problem. I am asking you simply, I guess, a mathematical question.

Assuming that my arguments have some foundation, some basis in real life, what would we need to add in order to get what I am shooting at?

Dr. **Wyngaarden**. We will be able to supply that, but it will take a little bit of research to do it, because of the costs of adding additional beds to the current census.

Mr. **O'Brien**. I am assuming that figure is somewhat less than what Mr. Conte was looking at?

Dr. **Wyngaarden**. I would hope so, sir.

Mr. **O'Brien**. That brings me back to square one, Doctor:

The sooner you could get me that information, I would be very appreciative.

Dr. **Wyngaarden**. Fine; it depends upon the mix of beds. There are some Institutes where the activity is more intense, and therefore the average cost is somewhat greater. We will have to see which are the areas where the beds are underutilized.

Mr. **O'Brien**. You don't need to dot every "i." Round figures is all I am shooting at.

Dr. **Wyngaarden**. We can supply the figures for average cost per bed in the various Institutes, occupancy rate, the ceilings, and from those, the figure you are after can be derived.

Mr. **Natcher**. Mr. Hoyer, I yield to you.

BUDGET REDUCTIONS

Mr. **Hoyer**. Thank you, Mr. Chairman.

Doctor, we went through $500 million for grants, $70 million for research centers, $90 million for biomedical research, a $22 million reduction for training grants and $125 million for contracts reduced, as I understand it?

I come to about $800 million, $807 million for those reductions. There would be an additional $200 million but as I understand it, it may be not included directly, so we may be comparing apples and oranges. Is that $200 for million AIDS research?

Dr. **Wyngaarden**. We had $144 million for AIDS in 1987.

Mr. HOYER. If you had that $144 million, which I understand was part of the $5.9, but is not part of the $4.9, is that correct, that accounts for some of it?

Dr. WYNGAARDEN. That is correct, and the difference is made up largely by the reduction for intramural research, which drops from $613 million to $548 million.

Mr. HOYER. So that applies.

Dr. WYNGAARDEN. That covers most of the difference.

MINORITY CONCERNS STRATEGY

Mr. HOYER. All right, Doctor, time constraints do not allow us to go through the budget thoroughly at this point in time. Let me go to a question that Congressman Stokes had. He had to leave, unfortunately, and asked me to ask it.

The former Administrator of the Alcohol, Drug Abuse and Mental Health Administration, Dr. Macdonald, now the Acting Assistant Secretary for Health, issued on November 7, 1985 a minority concerns strategy for ADAMHA.

In order to ensure that the goals outlined in that strategy are achieved, he instructed each Institute Director to initiate an accountability mechanism through the annual performance plans of all appropriate staff, especially Division Directors and Branch Chiefs, to ensure that these program activities are implemented.

Mr. Stokes' question to you is, do you believe that the development of a similar minority concerns strategy for NIH would be feasible and useful? If not, why not?

Dr. WYNGAARDEN. We have had that program for some time. The attention is included in the performance standards for each of our managers.

Mr. HOYER. Is there a name of that? Is there a document outlining the strategy?

Dr. WYNGAARDEN. For each individual in a management position, we have a series of performance standards, which are somewhat personalized. The minority concerns element is a component of each one of those standards, and each manager is evaluated each year on his or her attention to that activity.

Mr. HOYER. He has a second related question, if I might, and he would like to know:

Is there any reason why NIH could not implement a mechanism whereby the performance evaluations of senior level NIH officers, for the purposes of determining annual merit pay increases and bonuses, includes specific elements for achieving minority program and personnel goals, similar to the procedures established by ADAMHA?

I would presume your answer just made would cover that as well.

Dr. WYNGAARDEN. Yes, sir.

REORGANIZATION IN THE OFFICE OF RESEARCH SERVICES

Mr. HOYER. All right, time being short, let me reiterate Congressman Stokes' and my continuing concerns. I have read the executive summary dealing with the affirmative action program at NIH, an issue that was raised by Mr. Stokes and myself, and has been pursued by us.

I know that you are concerned about that, and I will look forward to seeing your detailed response to the findings.

Let me ask one specific question. One of the things that generated my concern, which I have noted previously, were Mr. Ducker's concerns with what was happening vis-a-vis himself and Dr. Becker. That may have been a personal problem.

As you know, GAO found there was no discrimination in that, and I was pleased to see that.

At the same time, we find reorganization has occurred going from two divisions to three divisions, essentially adopting a Safety Division, which put it into a separate division.

In this particular instance, you have gone from two divisions with a 50 percent representation by minority administrators to three divisions, two of which now have white, male directors, and the third of which has an acting director who is Dr. Becker, who is now heading essentially the post that Mr. Ducker headed up for some period of time. He has been in that acting capacity for 18 months now, perhaps longer.

Dr. WYNGAARDEN. I don't know how long it would be.

Mr. HOYER. For those who are concerned about this question, it would be easy to draw the conclusion that Dr. Becker remains in an acting capacity as well as his overall supervisory capacity of those three divisions, and thereby blocking any opportunity for an affirmative action step with respect to DAS, which had the only minority division head within NIH.

Doctor, that question may not require a response at this point in time, but it certainly does require a response in the detailed response you are going to give, and I would think that you would be concerned about that and give your attention to it, because if I were a minority woman, black, other minority within NIH, and I saw the percentage of white division chiefs going from 50 percent to 100 percent, one of which is acting, I would think to myself, GAO can tell me whatever they want, the facts of the case are that I am being shut out.

That is not a perception that you want to have, or that I want to have, and I would think that at the very least, Doctor, we ought to move on that position, and if Dr. Becker can perform it as well as his regular duties, then maybe we should go to three division chiefs directly under you.

Dr. WYNGAARDEN. Dr. Becker will be here to discuss some of the management actions within the ORS staff, and I think he would be the best person to explain that process to you. We have discussed it.

He discussed it with me before I assumed my position, and the rationale was that there were additional reorganizational steps that needed to be accomplished, and that he would be better able to perform this way. Rather than having a new director who would need to make certain changes, which is always hard for a new person to do, Dr. Becker would take the onus upon himself, and then proceed to make a permanent appointment.

Mr. HOYER. Certainly, accomplishing part of the objective and taking some of the onus.

Dr. WYNGAARDEN. Dr. Malone may have additional comments.

COMMITTEE INVESTIGATION

Dr. MALONE. I think Dr. Becker can answer for himself. The House Appropriations Committee Investigations staff performed a detailed investigation last year, and it ought to be reiterated that, in the rather detailed investigation, some of the original allegations were put completely asunder.

It was clear to me in reading their report that what Dr. Becker did was essentially designed to create a more efficient organization to provide services to NIH. Beyond that, Dr. Becker can best defend the rationale for the organizational changes.

Dr. WYNGAARDEN. I would only add one additional point, Mr. Hoyer, and that is that Dr. Becker was appointed by Dr. Fredrickson to that position before I arrived, in response to a great deal of dissatisfaction within NIH on the part of the scientists regarding the efficiency with which research services were provided. It was perceived to be a position that required someone with senior managerial strengths, and also someone who had grown up within the intramural NIH, who understood all those problems.

Dr. Becker was selected for that position. The charge from Dr. Fredrickson was broad but also quite precise: to improve the delivery of services for the conduct of science, which is our primary objective.

That charge must be met with a great deal of sensitivity for people who are affected by any changes, and as I have observed Dr. Becker in this role now for four years, I think he does that admirably.

It is not possible to make changes in an organization as complex as ours without at times creating some concern, and where minority issues are involved, the concern is sometimes great.

I think the GAO report was a gratifying one to us in many respects, and also very useful to us in those respects where they found some shortcomings. I can assure you we are taking those seriously in addressing the problems.

Mr. HOYER. I appreciate your responses. I will look forward to your written response, also.

Dr. WYNGAARDEN. Be happy to supply any additional information you might like.

PEER REVIEW SYSTEM

Mr. NATCHER. Dr. Wyngaarden, are you planning to make any changes in the peer review system?

Dr. WYNGAARDEN. No fundamental changes are planned. We have considered at one of our Director's Advisory Committee meetings last year the whole process of extramural awards. We looked at any areas that might possibly be improved in the peer review system; we did discover a greater reluctance than we think advisable at present to fund equipment.

We have fallen a bit behind in the proportionate increase for equipment in our research project grants; it is not as large a fraction of the budget as it was 10 or 20 years ago. We have issued some general advice, through the managers of the Division of Research Grants to the study sections, to look more favorably, or at least more carefully, on equipment needs.

We believe we need to be a bit more generous in that regard. In addition, we did ask the councils to review actions of study sections where they might appear to have reduced the number of years of recommended support without justification.

It has become a reflex response to reduce first-time applications to 3 years of support, and we think that some of those reductions were not adequately documented. Consequently, the Councils have been looking at this reduction of support, and in some cases lengthening the award.

These are minor tune-ups, the sort of thing that goes on year after year. We think we might need a little bit of advice from the Directors' Advisory Committee, but we remain very, very pleased with the performance of the peer review system.

IMPACT OF SEQUESTRATION

Mr. **Natcher**. Dr. Wyngaarden, I want to turn your attention to the impact of sequestration after March 1. Under the Gramm-Rudman-Hollings Act, your 1986 appropriations are cut by 4.3 percent, $230 million.

Have any programs been reduced below the 1986 budget request? Have any of them been reduced below that point?

Dr. **Wyngaarden**. No; none of the programs has been reduced below the 1986 request level.

1987 BUDGET REQUEST

Mr. **Natcher**. To what extent, Dr. Wyngaarden, are the 1986 cuts restored in 1987?

Dr. **Wyngaarden**. The 1987 budget is $131 million less than the comparable 1986, so in most of those areas the cuts are not restored.

There are two budgets in 1987 that are somewhat better protected than the others. They are the Library of Medicine and the intramural program. However, the latter, when compared with 1985, undergoes the same reduction as the extramural program.

I should also mention the AIDS budget has been protected from any cut.

REPROGRAMMING REQUESTS

Mr. **Natcher**. Do you plan to submit reprogramming requests to redistribute any of the 1986 Gramm-Rudman cuts?

Dr. **Wyngaarden**. We have discussed this as a possible adjustment. We have no reprogramming requests ready for submission. We have not decided positively to do this, but in discussion with a few Institutes, that possibility has been raised as an adjustment that might be proposed later in the fiscal year.

CONSOLIDATION OF AIDS FUNDING

Mr. **Natcher**. Dr. Wyngaarden, the 1987 budget consolidates all AIDS funding in the Office of the Assistant Secretary of Health. Do you know how much of this will be allocated to NIH?

Dr. **Wyngaarden**. No, sir, we don't know that. I have verbal assurance from the Department that the commitment requests that would be generated by the adjusted 1986 request of $120 million would be honored within the 1987 appropriations, if that is made at the President's requested level.

Mr. **Natcher**. Who will decide, Dr. Wyngaarden, how these funds will be allocated, and how much influence will the NIH Director have on the decision?

Dr. **Wyngaarden**. I have not heard the mechanism discussed. It will be done within the Office of the Assistant Secretary. I would hope we have some input, but I am not aware that a mechanism has been established.

RESEARCH PROJECT GRANTS

Mr. **Natcher**. Now, as to the number of competing research projects funded in 1986, section 202 of the 1986 Appropriations Act requires you to fund at least 6,100 competing research projects.

Under Gramm-Rudman, your 1986 appropriation is reduced by $236,243,000. Dr. Wyngaarden, is it your position that you are still required to fund 6,100 competing projects?

Dr. **Wyngaarden**. Yes, sir.

Mr. **Natcher**. Do you have a General Counsel's opinion as to this particular matter?

Dr. **Wyngaarden**. We sought the opinion of the Public Health Service and the Department, and that was their judgment. I am not sure just whom they consulted to consolidate that impression.

Mr. **Natcher**. If you will, Doctor, at this point in the record, give us a table for the years 1978-1987, showing for each Institute the total amount appropriated for research project grants, the number of grants and the average grant, and place that in the record at this point for us.

In addition, give us a table for the same years which breaks out indirect and direct costs separately and place that in the record for us.

[The information follows:]

DHHS - National Institutes of Health

Research Project Grants

(Dollars in thousands)

	1978 Actual			1979 Actual			1980 Actual			1981 Actual		
	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost
NCI												
Noncompeting.....	1395	$156,420	$112.1	1497	$167,616	$112.0	1766	$219,020	$124.0	1614	$245,574	$135.4
Admin. supp......	(156)	6,506		(208)	10,519		(191)	10,025		(236)	8,635	
Competing........	886	91,035	102.7	901	109,549	121.6	773	92,281	119.4	814	101,246	124.4
Subtotal.......	2281	253,961		2398	287,684		2539	321,326		2628	355,455	
NHLBI												
Noncompeting.....	1329	139,858	105.2	1491	163,391	109.6	1735	198,330	114.3	1582	200,902	127.0
Admin. supp......	(138)	1,781		(103)	1,297		(138)	2,088		(66)	1,455	
Competing........	759	67,553	89.0	942	88,790	94.3	589	66,478	112.9	774	86,484	111.7
Subtotal.......	2088	209,192		2433	253,478		2324	266,896		2356	288,841	
NIDR												
Noncompeting.....	209	13,564	64.9	261	18,959	72.6	273	20,177	73.9	226	17,845	79.0
Admin. supp......	(4)	191		(3)	175		(1)	41		(7)	358	
Competing........	144	10,306	71.6	131	8,091	61.8	97	7,600	78.4	143	13,047	91.2
Subtotal.......	353	24,061		392	27,225		370	27,818		369	31,250	
NIDDK												
Noncompeting.....	1273	105,908	83.2	1474	124,777	84.7	1678	157,201	93.7	1698	173,030	101.9
Admin. supp......	(87)	1,035		(54)	1,043		(70)	1,459		(70)	1,632	
Competing........	685	52,241	76.3	769	62,975	81.9	698	61,023	87.4	759	74,354	98.0
Subtotal.......	1958	159,184		2243	188,795		2376	219,683		2457	249,016	

Research Project Grants - cont'd.

	1978 Actual			1979 Actual			1980 Actual			1981 Actual		
	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost
NINCDS												
Noncompeting.....	559	42,821	76.6	768	55,312	72.0	1014	80,260	79.2	989	94,969	96.0
Admin. supp......	(41)	555		(23)	510		(36)	774		(28)	1,504	
Competing........	534	35,522	66.5	577	46,232	80.1	503	51,581	102.5	487	51,820	106.4
Subtotal.......	1093	78,898		1345	102,054		1517	132,615		1476	148,293	
NIAID												
Noncompeting.....	641	54,110	84.4	768	68,577	89.3	1001	92,223	92.1	1087	105,095	96.7
Admin. supp......	(14)	506		(21)	526		(14)	1,141		(17)	514	
Competing........	397	31,059	78.2	537	42,951	80.0	452	39,130	86.6	433	44,713	103.3
Subtotal.......	1038	85,675		1305	112,054		1453	132,494		1520	150,322	
NIGMS												
Noncompeting.....	1180	89,746	76.1	1378	112,468	81.6	1892	151,569	80.1	2098	178,102	84.9
Admin. supp......	(20)	556		(32)	789		(29)	848		(34)	647	
Competing........	788	58,232	73.9	1020	76,219	74.7	890	78,563	88.3	711	74,752	105.1
Subtotal.......	1968	148,534		2398	189,476		2782	230,980		2809	253,501	
NICHD												
Noncompeting.....	552	51,162	92.7	747	67,153	89.9	879	83,652	95.2	795	83,528	105.1
Admin. supp......	(49)	1,872		(36)	924		(30)	1,082		(32)	680	
Competing........	453	34,212	75.5	461	40,918	88.8	348	32,613	93.7	453	44,897	99.1
Subtotal.......	1005	87,246		1208	108,995		1227	117,347		1248	129,105	
NEI												
Noncompeting.....	433	30,230	69.8	581	42,630	73.4	689	55,314	80.3	605	55,241	91.3
Admin. supp......	(69)	2,026		(83)	2,890		(58)	751		(52)	906	
Competing........	350	24,422	69.8	301	25,117	83.4	217	20,020	92.3	304	28,890	95.0
Subtotal.......	783	56,678		882	70,637		906	76,085		909	85,037	

Research Project Grants - cont'd.

	1978 Actual			1979 Actual			1980 Actual			1981 Actual		
	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost
NIEHS												
Noncompeting.....	144	13,554	94.1	231	19,677	85.2	202	19,142	94.8	184	20,741	112.7
Admin. supp......	(2)	195		(3)	18		(8)	699		(10)	557	
Competing........	119	9,083	76.3	91	8,907	97.9	87	8,529	98.0	113	11,568	102.4
Subtotal.......	263	22,832		322	28,602		289	28,370		297	32,866	
NIA												
Noncompeting.....	154	13,502	87.7	195	18,247	93.6	284	24,692	86.9	293	29,588	101.0
Admin. supp......	(8)	105		(9)	97		(4)	79		(5)	101	
Competing........	85	7,185	84.5	214	15,724	73.5	131	14,666	112.0	118	13,265	112.4
Subtotal.......	239	20,792		409	34,068		415	39,437		411	42,954	
NIAMSD												
Noncompeting.....	--	---	---	--	---	---	--	---	---	--	---	---
Admin. supp......	--	---		--	---		--	---		--	---	
Competing........	--	---	---	--	---	---	--	---	---	--	---	---
Subtotal.......	--	---		--	---		--	---		--	---	
TOTAL NIH												
Noncompeting.....	7869	710,875	90.3	9391	858,807	91.5	11413	1,101,580	96.5	11371	1,204,615	105.9
Admin. supp......	(588)	15,328		(575)	18,788		(579)	18,987		(557)	16,989	
Competing........	5200	420,850	80.9	5944	525,473	88.4	4785	472,484	98.7	5109	545,036	106.7
Total..........	13069	1,147,053		15335	1,403,068		16198	1,593,051		16480	1,766,640	

Research Project Grants - cont'd.

	1982 Actual			1983 Actual			1984 Actual			1985 Actual		
	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost
NCI												
Noncompeting.....	1806	254,377	$140.9	1927	287,425	$149.2	1877	292,544	$155.9	1975	340,245	$172.3
Admin. supp......	(142)	7,250		(106)	6,439		(188)	11,068		(161)	7,766	
Competing........	748	96,775	129.4	886	111,896	126.3	969	157,635	162.7	1017	168,464	165.6
Subtotal.......	2554	358,402		2813	405,760		2846	461,247		2992	516,475	
NHLBI												
Noncompeting.....	1516	203,694	134.4	1689	238,967	141.5	1674	287,987	172.0	1737	319,736	184.1
Admin. supp......	(63)	1,490		(20)	739		(24)	591		(38)	1,226	
Competing........	765	99,733	130.4	748	116,989	156.4	852	119,808	140.6	901	158,203	175.6
Subtotal.......	2281	304,917		2437	356,695		2526	408,386		2638	479,165	
NIDR												
Noncompeting.....	254	22,664	89.2	253	23,836	94.2	266	28,581		266	31,198	117.3
Admin. supp......	(1)	41		(2)	57		(2)	116		(1)	70	
Competing........	108	10,402	96.3	133	13,505	101.5	123	13,438	109.3	131	15,859	121.1
Subtotal.......	362	33,107		386	37,398		389	42,135		397	47,127	
NIDDK												
Noncompeting.....	1677	178,080	106.2	1645	191,782	116.6	1682	220,207	130.9	1439	206,678	143.6
Admin. supp......	(86)	2,152		(89)	3,172		(62)	2,703		(77)	7,215	
Competing........	645	68,300	105.9	777	87,331	112.4	785	96,542	123.0	596	80,921	135.8
Subtotal.......	2322	248,532		2422	282,285		2467	319,452		2035	294,814	

Research Project Grants - cont'd.

	1982 Actual			1983 Actual			1984 Actual			1985 Actual		
	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost
NINCDS												
Noncompeting.....	995	104,833	105.4	1074	128,094	119.3	1098	136,969	124.7	1144	148,144	129.5
Admin. supp......	(32)	1,152		(19)	469		(39)	1,247		(36)	3,412	
Competing........	500	52,921	105.8	539	53,479	99.2	564	70,907	125.7	722	105,978	146.8
Subtotal.......	1495	158,906		1613	182,042		1662	209,123		1866	257,534	
NIAID												
Noncompeting.....	1012	108,431	107.1	1009	120,047	119.0	1098	145,210	132.2	1166	172,554	148.0
Admin. supp......	(11)	639		(8)	673		(12)	390		(18)	667	
Competing........	411	43,918	106.9	522	59,910	114.8	507	61,252	120.8	549	72,045	131.2
Subtotal.......	1423	152,988		1531	180,630		1605	206,852		1715	245,266	
NIGMS												
Noncompeting.....	1758	175,506	99.8	1820	202,431	111.2	2021	251,895	124.6	1907	259,990	136.3
Admin. supp......	(21)	1,070		(29)	1,027		(21)	593		(75)	2,998	
Competing........	859	90,834	105.7	835	92,760	111.1	702	89,322	127.2	987	133,845	135.6
Subtotal.......	2617	267,410		2655	296,218		2723	341,810		2894	396,833	
NICHD												
Noncompeting.....	797	87,196	109.4	892	105,225	118.0	920	116,204	126.3	898	119,672	133.3
Admin. supp......	(40)	739		(41)	1,599		(48)	1,205		(78)	3,732	
Competing........	439	44,194	100.7	452	45,852	101.4	415	51,835	124.9	469	64,200	136.9
Subtotal.......	1236	132,129		1344	152,676		1335	169,244		1367	187,604	
NEI												
Noncompeting.....	677	64,293	95.0	729	77,665	106.5	660	78,578	119.1	701	84,646	120.8
Admin. supp......	(48)	779		(44)	1,427		(57)	1,642		(49)	1,348	
Competing........	273	26,910	98.6	247	25,930	105.0	309	35,387	114.5	367	47,230	128.7
Subtotal.......	950	91,982		976	105,022		969	115,607		1068	133,224	

Research Project Grants - cont'd.

	1982 Actual			1983 Actual			1984 Actual			1985 Actual		
	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost
NIEHS												
Noncompeting.....	206	23,624	114.7	226	25,030	110.8	211	30,669	145.4	234	35,565	152.0
Admin. supp......	(21)	1,303		(15)	434		(10)	789		(7)	443	
Competing........	104	10,927	105.1	98	14,717	150.2	138	16,481	119.4	108	16,624	153.9
Subtotal.......	310	35,854		324	40,181		349	47,939		342	52,632	
NIA												
Noncompeting.....	245	28,765	117.4	268	34,848	130.0	305	47,745	156.5	269	49,787	185.1
Admin. supp......	(6)	169		(12)	334		(15)	704		(26)	989	
Competing........	175	19,706	112.6	152	21,027	138.3	129	19,309	149.7	209	30,895	147.8
Subtotal.......	420	48,640		420	56,209		434	67,758		478	81,671	
NIAMSD												
Noncompeting.....	--	---	---	--	---	---	--	---	---	375	53,087	141.6
Admin. supp......	--	---		--	---		--	---		(15)	632	
Competing........	--	---	---	--	---	---	--	---	---	190	23,835	125.4
Subtotal.......	--	---		--	---		--	---		565	77,554	
TOTAL NIH												
Noncompeting.....	10943	1,251,463	114.4	11532	1,435,350	124.5	11812	1,636,589	138.6	12111	1,821,302	150.4
Admin. supp......	(471)	16,784		(385)	16,370		(478)	21,048		(581)	30,498	
Competing........	5027	564,620	112.3	5389	643,396	119.4	5493	731,916	133.2	6246	918,099	147.0
Total..........	15970	1,832,867		16921	2,095,116		17305	2,389,553		18357	2,769,899	

Research Project Grants - cont'd.

	1986 Appropriation			1986 Appropriation After Sequestration			1986 Revised			1987 Estimate		
	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost	No.	Amount	Avg. Cost
NCI												
Noncompeting.....	2151	$406,861	$189.1	2151	$389,366	$181.0	2151	$389,366	$181.0	2050	$381,489	$186.1
Admin. supp......	(152)	6,575		(152)	6,292		(152)	6,292		(152)	6,575	
Competing........	931	175,707	188.7	931	168,312	180.8	857	161,512	188.5	874	149,070	170.6
Subtotal.......	3082	589,143		3082	563,970		3008	557,170		2924	537,134	
NHLBI												
Noncompeting.....	1822	370,194	203.2	1822	354,276	194.4	1822	354,276	194.4	1803	352,109	195.3
Admin. supp......	(35)	1,162		(35)	1,112		(35)	1,112		(35)	1,162	
Competing........	886	162,378	183.3	886	155,423	175.4	817	143,954	176.2	802	145,635	181.6
Subtotal.......	2708	533,734		2708	510,811		2639	499,342		2605	498,906	
NIDR												
Noncompeting.....	248	28,926	116.6	248	27,682	111.6	248	27,682	111.6	269	30,561	113.6
Admin. supp......	--	---		--	---		--	---		--	---	
Competing........	149	18,083	121.4	149	17,309	116.2	149	17,309	116.2	110	12,683	115.3
Subtotal.......	397	47,009		397	44,991		397	44,991		379	43,244	
NIDDK												
Noncompeting.....	1407	218,322	155.2	1407	208,934	148.5	1407	208,934	148.5	1361	207,080	152.2
Admin. supp......	(66)	4,338		(66)	4,151		(66)	4,151		(46)	1,436	
Competing........	637	97,283	152.7	637	93,212	146.3	564	86,756	153.8	566	82,627	146.0
Subtotal.......	2044	319,943		2044	306,297		1971	299,841		1927	291,143	

Research Project Grants - cont'd.

	1986 Appropriation			1986 Appropriation After Sequestration			1986 Revised			1987 Estimate		
	No.	Amount	Ave. Cost	No.	Amount	Ave. Cost	No.	Amount	Ave. Cost	No.	Amount	Ave. Cost
NINCDS												
Noncompeting.....	1273	188,114	147.8	1273	180,025	141.4	1273	180,025	141.4	1313	188,941	143.9
Admin. supp......	(33)	1,000		(33)	957		(33)	957		(23)	668	
Competing........	646	105,159	162.8	646	100,637	155.8	598	91,083	152.3	538	80,126	148.9
Subtotal.......	1919	294,273		1919	281,619		1871	272,065		1851	269,735	
NIAID												
Noncompeting.....	1197	179,582	150.0	1197	171,860	143.6	1197	173,451	144.9	1178	171,293	145.4
Admin. supp......	(16)	573		(16)	548		(16)	548		(16)	524	
Competing........	527	77,168	146.4	527	73,874	140.2	465	70,770	152.2	421	58,126	138.1
Subtotal.......	1724	257,323		1724	246,282		1662	244,769		1599	229,943	
NIGMS												
Noncompeting.....	1971	290,228	147.2	1971	277,748	140.9	1971	278,918	141.5	2082	292,509	140.5
Admin. supp......	(17)	675		(17)	646		(17)	633		(17)	703	
Competing........	972	138,792	142.8	972	132,874	136.7	810	124,359	153.5	689	100,867	146.4
Subtotal.......	2943	429,695		2943	411,268		2781	403,910		2771	394,079	
NICHD												
Noncompeting.....	891	130,271	146.2	891	124,669	139.9	891	123,919	139.1	913	125,465	137.4
Admin. supp......	(40)	1,272		(40)	1,217		(40)	1,217		(40)	1,340	
Competing........	483	67,668	140.1	483	64,779	134.1	467	64,379	137.9	456	62,826	137.8
Subtotal.......	1374	199,211		1374	190,665		1358	189,515		1369	189,631	
NEI												
Noncompeting.....	783	101,469	129.6	783	97,106	124.0	783	95,072	121.4	853	101,642	119.2
Admin. supp......	(45)	880		(45)	842		(45)	842		(38)	1,750	
Competing........	358	47,066	131.5	358	45,046	125.8	331	41,856	126.5	250	33,869	135.5
Subtotal.......	1141	149,415		1141	142,994		1114	137,770		1103	137,261	

Research Project Grants - cont'd.

	1986 Appropriation			1986 Appropriation After Sequestration			1986 Revised			1987 Estimate		
	No.	Amount	Ave. Cost	No.	Amount	Ave. Cost	No.	Amount	Ave. Cost	No.	Amount	Ave. Cost
NIEHS												
Noncompeting.....	247	39,173	158.6	247	37,489	151.8	247	37,489	151.8	229	37,098	162.0
Admin. supp......	(10)	528		(10)	505		(10)	505		(10)	514	
Competing........	111	16,931	152.5	111	16,203	146.0	111	16,203	146.0	105	15,301	145.7
Subtotal.......	358	56,632		358	54,197		358	54,197		334	52,913	
NIA												
Noncompeting.....	303	60,130	198.4	303	57,544	189.9	303	57,544	189.9	345	60,618	175.7
Admin. supp......	(8)	128		(8)	123		(8)	123		(8)	128	
Competing........	201	32,442	161.4	201	31,104	154.7	177	28,425	160.6	145	23,502	162.1
Subtotal.......	504	92,700		504	88,771		480	86,092		490	84,248	
NIAMSD												
Noncompeting.....	383	55,947	146.1	383	53,541	139.8	383	53,541	139.8	389	54,702	140.6
Admin. supp......	(13)	375		(13)	359		(13)	359		(14)	400	
Competing........	199	27,277	137.1	199	26,130	131.3	173	24,606	142.2	148	19,909	134.5
Subtotal.......	582	83,599		582	80,030		556	78,506		537	75,011	
TOTAL NIH												
Noncompeting.....	12676	2,069,217	163.2	12676	1,980,240	156.2	12676	1,980,217	156.2	12785	2,003,507	156.7
Admin. supp......	(435)	17,506		(435)	16,752		(435)	16,739		(399)	15,200	
Competing........	6100	965,954	158.4	6100	924,903	151.6	5519	871,212	157.9	5104	784,541	153.7
Total..........	18776	3,052,677		18776	2,921,895		18195	2,868,168		17889	2,803,248	

DHHS-National Institutes of Health

STATISTICAL DATA - RESEARCH GRANTS 1/
PERCENTAGE OF INDIRECT COSTS TO TOTAL DOLLARS AWARDED

(Dollars in thousands)

Fiscal Year	Dollars	Indirect Costs Awarded	Percentage
1978................	$1,529,066	$416,093	27.2
1979................	1,844,001	512,279	27.8
1980................	2,050,074	586,306	28.6
1981................	2,224,138	655,143	29.5
1982................	2,300,534	689,855	30.0
1983................	2,584,787	791,580	30.6
1984................	2,958,266	921,627	31.2
1985................	3,412,923	1,069,707	31.3
1986 Estimate.......	3,478,055	1,106,021	31.8
1987 Pres. Budget 2/ Request (With Cap)	3,394,830	1,038,818	30.6
(Without Cap)....	3,479,830	1,123,818	32.3

1/ Actual data from the Indirect Cost Management System (ICMS).

2/ Excludes AIDS funding.

INCREASES FOR FULL INDIRECT COSTS

Mr. NATCHER. Give us, if you will please, a table showing the amounts which would have to be added to your 1987 budget in order to pay full indirect costs, number one.

Number two, pay full direct costs on research project grants with normal negotiated reductions from study section recommendations, on competing grants and full commitment levels on non-competing projects, and also, Doctor, same as number two, for 6100 competing projects, and place that in the record for us.

[The information follows:]

DHHS-National Institutes of Health

ADDITIONAL AMOUNT REQUIRED TO PAY FULL INDIRECT COSTS AT THE FY 1987 PRESIDENTS'S BUDGET LEVEL

(Dollars in thousands)

	FY 1987 President's Budget		Additional Amount Required	Total	
	No.	Amount	Amount	No.	Amount
Res. Proj. Grants...					
Noncomp...........	12,785	$2,003,507	$51,425	12,785	$2,054,932
Adm. Sups.........	(399)	15,200	77	(399)	15,277
Competing.........	5,104	784,541	20,605	5,104	805,146
Total RPGs......	17,889	2,803,248	72,107	17,889	2,875,355
Centers.............	523	447,222	7,588	523	454,810
Other Research......	2,301	237,534	1,749	2,301	239,283
Training............	9,258	198,204	---	9,258	198,204
Contracts...........	1,192	328,458	3,186	1,192	331,644
Intramural Res......		548,357	---		548,357
Res. Manag. & Sup...		210,894	---		210,894
Control/Construct...		61,131	200		61,331
NLM.................		56,408	170		56,578
OD..................		36,701	---		36,701
B&F.................		8,000	---		8,000
Total, NIH........		4,936,157	85,000		5,021,157

DHHS-National Institutes of Health

ADDITIONAL AMOUNTS REQUIRED OVER THE FY 1987 PRESIDENT'S BUDGET TO SUPPORT 5,104 COMPETING GRANTS AT FULL INDIRECT COSTS WITH BOTH NONCOMPETING AND COMPETING AWARDS FUNDED AT HISTORICAL LEVELS

(Dollars in thousands)

	FY 1987 President's Budget		Additional Amount Required	Total	
	No.	Amount		No.	Amount
Noncomp...........	12,785	$2,003,507	$250,916	12,785	$2,254,423
Adm. Sups.........	(399)	15,200	1,500	(399)	16,700
Competing.........	5,104	784,541	116,181	5,104	900,722
Total RPGS......	17,889	2,803,248	368,597	17,889	3,171,845

ADDITIONAL AMOUNTS REQUIRED OVER THE FY 1987 PRESIDENT'S BUDGET TO SUPPORT 6,100 COMPETING GRANTS AT FULL INDIRECT COSTS WITH BOTH NONCOMPETING AND COMPETING AWARDS FUNDED AT HISTORICAL LEVELS

(Dollars in thousands)

	FY 1987 President's Budget		Additional Amount Required		Total	
	No.	Amount	No.	Amount	No.	Amount
Res. Proj. Grants...						
Noncomp...........	12,785	$2,003,507	---	$250,916	12,785	$2,254,423
Adm. Sups.........	(399)	15,200	---	1,500	(399)	16,700
Competing.........	5,104	784,541	996	268,388	6,100	1,052,929
Total RPGs......	17,889	2,803,248	996	519,304	18,885	3,324,052

TOP 20 INSTITUTIONS AND NIH STAFFING

Mr. NATCHER. Update the table on page 71 of last year's hearing, and we will appreciate it. Also, update the tables on pages 91 through 93 of last year's hearings.

Dr. WYNGAARDEN. We will be happy to do that, Mr. Chairman.

[The information follows:]

DHHS-National Institutes of Health

TOP 20 RECIPIENTS OF NIH RESEARCH GRANT SUPPORT IN 1985

(Dollars in thousands)

	Institution	Location	Direct Cost	Indirect Cost	Total
1.	Johns Hopkins University	Baltimore, MD	$57,125	$31,970	$89,095
2.	University of California, San Francisco	San Francisco, CA	63,871	17,409	81,280
3.	Columbia University	New York, NY	43,064	28,438	71,502
4.	Yale University	New Haven, CT	44,365	27,076	71,441
5.	Stanford University	Stanford, CA	43,812	27,218	71,030
6.	University of Washington	Seattle, WA	52,666	18,220	70,886
7.	University of Pennsylvania	Philadelphia, PA	44,055	24,901	68,956
8.	Harvard University	Cambridge, MA	40,750	28,176	68,926
9.	University of California, Los Angeles	Los Angeles, CA	46,558	18,196	64,754
10.	University of Minnesota	Minneapolis, MN	41,195	14,846	56,041
11.	Washington University	Saint Louis, MO	38,240	17,106	55,346
12.	University of Wisconsin, Madison	Madison, WI	39,219	14,892	54,111
13.	Yeshiva University	New York, NY	28,673	22,870	51,543
14.	University of Michigan	Ann Arbor, MI	34,471	15,881	50,352
15.	University of California, San Diego	San Diego, CA	37,302	12,510	49,812
16.	Duke University	Durham, NC	32,707	15,044	47,751
17.	Cornell University	Ithaca, NY	29,427	13,643	43,070
18.	University of Chicago	Chicago, Il	26,476	16,424	42,900
19.	Massachusetts Institute of Technology	Cambridge, MA	26,708	14,622	41,330
20.	University of New York Medical Center	New York, NY	24,702	15,754	40,456
			795,386	395,196	1,190,582

DHHS-National Institutes of Health

FULL TIME PERMANENT STAFFING
FY 1977 - 1986

	FY 1977	FY 1978	FY 1979	FY 1980	FY 1981	FY 1982 1/	FY 1983 1/	FY 1984	FY 1985	FY 1986 as of 2/15/86
NCI										
Intramural Research	1,429	1,431	1,426	1,306	1,280	1,237	1,208	1,159	1,102	1,114
Res. Mgmt. & Support	474	475	483	467	467	425	444	442	395	399
Cancer Control	52	55	55	51	51	44	79	97	99	97
Total	1,955	1,961	1,964	1,824	1,798	1,706	1,731	1,698	1,596	1,610
NHLBI										
Intramural Research	369	383	361	363	327	259	261	249	245	247
Res. Mgmt. & Support	354	387	375	373	338	379	378	387	385	379
Total	723	770	736	736	665	638	639	636	630	626
NIDR										
Intramural Research	217	219	171	166	141	136	132	153	153	144
Res. Mgmt. & Support	59	64	104	105	105	103	92	60 2/	63	64
Total	276	283	275	271	246	239	224	213	216	208
NIADDK										
Intramural Research	456	466	458	445	375	304	309	304	283	282
Res. Mgmt. & Support	129	164	160	161	173	195	174	183	172	169
Total	585	630	618	606	548	499	483	487	455	451
NINCDS										
Intramural Research	318	321	303	307	270	244	233	252	241	245
Res. Mgmt. & Support	207	225	211	203	208	214	210	202	191	192
Total	525	546	514	510	478	458	443	454	432	437
NIAID										
Intramural Research	478	483	477	481	439	376	361	358	346	348
Res. Mgmt. & Support	143	151	139	144	150	163	165	173	167	175
Total	621	634	616	625	589	539	526	531	513	523

	FY 1977	FY 1978	FY 1979	FY 1980	FY 1981	FY 1982	FY 1983	FY 1984	FY 1985	FY 1986 as of 2/15/86
NIGMS										
Intramural Research	0	0	0	0	0	0	0	0	0	0
Res. Mgmt. & Support	159	164	161	149	147	140	140	132	130	129
Total	159	164	161	149	147	140	140	132	130	129
NICHD										
Intramural Research	189	201	203	192	136	151	150	150	145	144
Res. Mgmt. & Support	160	170	158	176	185	179	183	174	163	157
Total	349	371	361	368	321	330	333	324	308	301
NEI										
Intramural Research	98	103	111	114	85	93	92	88	87	85
Res. Mgmt. & Support	45	53	57	55	52	57	63	65	58	56
Total	143	156	168	169	137	150	155	153	145	141
NIEHS										
Intramural Research	254	279	287	334	358	394	442	428	414	426
Res. Mgmt. & Support	54	66	67	71	72	67	68	71	75	77
Total	308	345	354	405	430	461	510	499	489	503
NIA										
Intramural Research	152	172	184	188	163	155	152	163	155	161
Res. Mgmt. & Support	39	55	58	81	101	93	98	94	96	95
Total	191	227	242	269	264	248	250	257	251	256
NIH										
Intramural Research	3,960	4,058	3,981	3,896	3,574	3,349	3,340	3,277	3,171	3,196
Res. Mgmt. & Support	1,823	1,974	1,973	1,985	1,998	2,015	2,015	2,010	1,895	1,892
Cancer Control	52	55	55	51	51	44	79	97	99	97
Subtotal NIH	5,835	6,087	6,009	5,932	5,623	5,408	5,434	5,384	5,165	5,185

	FY 1977	FY 1978	FY 1979	FY 1980	FY 1981	FY 1982	FY 1983	FY 1984	FY 1985	FY 1986 as of 2/15/86
DRR	75	79	71	74	78	79	77	77	74	75
FIC	45	48	35	31	42	45	45	49	50	47
NLM	466	490	456	428	474	468	464	482	476	451
OD	1,797 3/	1,794 3/	517	504	516	512	519	513	500	479
Central Services	2,798	2,848	4,028 3/	4,035	4,034	3,958	4,068	4,106	3,972	3,927
Total NIH	11,016	11,346	11,116	11,004	10,767	10,470	10,607	10,611	10,237	10,164

1/ The major portion of the decrease from 1980 to 1981 and 1982 is due to the reclassification of Service Fellows from the full-time-permanent employment category to the other-than-full-time-permanent employment category.

2/ Reflects an internal reorganization between program budget activities.

3/ During FY 1976-1978 most of the functions of the current Office of Research Services was part of the Office of Administration and in our historical records included as part of the Office of the Director instead of Central Services. For 1979-1985, the positions are included in Central Services.

NOTE: Due to transfers of programs between Institutes and internal reorganizations the numbers in all years are not comparable.

Mr. NATCHER. Mr. O'Brien, I yield to you.

Mr. O'BRIEN. Thank you, Mr. Chairman.

I have no further questions.

Mr. NATCHER. Dr. Wyngaarden, we want to thank you for your appearance before our committee at this time in behalf of the budget request for the National Institutes of Health. This has been a good hearing, Dr. Wyngaarden. We want you to know that we appreciate it, and we are looking forward to the hearings with the individual institutes.

The committee will now adjourn until 10:00 in the morning.

[The following questions were submitted to be answered for the record:]

DOWNWARD NEGOTIATIONS

Mr. Natcher. Your budget proposes downward negotiations of about 6 percent from full study section recommended amounts for competing awards and committed levels for noncompeting continuations in FY 1986 and downward negotiations of 11 percent in FY 1987. Are these average reductions or will the same percentage reduction be applied to each grant?

Dr. Wyngaarden. The resources provided in FY 1986 will permit a 5 percent increase over FY 1985, requiring a 6 percent downward negotiation. The FY 1987 request will provide a 2 percent increase over FY 1986, requiring a 11 percent downward negotiation. The required negotiations vary among the Institutes and will also vary with individual grants.

Mr. Natcher. If the 1986 proposed rescissions are not approved, will this affect the downward negotiation policy in either FY 1986 or FY 1987?

Dr. Wyngaarden. Downward negotiations would increase from 6.7 percent under the FY 1986 revised budget to 9.3 percent without the rescission. This change is largely due to an increased number of competing grants that would be funded if the rescission were not implemented. Because of the increase in the number of noncompeting grants generated by the additional competing grants in 1986, the level of negotiations would increase in 1987.

EFFECT OF RESCISSION ON FY 1987 BUDGET

Mr. Natcher. How would failure of Congress to approve your FY 1986 rescission proposals affect your FY 1987 budget?

Dr. Wyngaarden. The FY 1986 rescission proposes to reduce research project grants by $53.7 million and 581 competing awards, and to reduce the small and minority universities and colleges program by $9.1 million. If Congress does not approve the proposed rescission, additional commitments in these two programs would be generated in 1987. To offset these additional costs, the number of competing research project grants would be reduced.

GRANT REDUCTIONS

Mr. Natcher. In your own professional judgment, how far is it wise to go in reducing costs of individual grants in order to permit funding of additional projects?

Dr. Wyngaarden. We believe that decreasing grant budgets by more than 10 percent from recommended levels could lead to severe disruptions in the investigators' ability to perform the approved research. While investigators with larger grants, such as program and center projects, might be able to accomplish essential functions by rebudgeting within available funds, most investigators would need to reduce important support and professional staffs and to forego expenditures for some otherwise essential equipment, supplies, travel, and patient and animal work. These limitations could disrupt the grantees' ability to accomplish research goals and thus impede scientific progress of the projects. While these sequelae could be minimized by not negotiating so drastically on individual grants, the alternative choice of funding fewer grants in the aggregate could similarly limit advances in biomedical sciences and knowledge.

Mr. Natcher. Stated in another way, if additional funds were to become available in FY 1987, would you use the money to fund more projects, or would you use it to more fully fund the 17,899 projects carried in the budget request?

Dr. Wyngaarden. If additional funds were to become available for FY 1987, our first priority would be to more fully fund 17,889 research project grants reflected in the FY 1987 request. This preference is in keeping with NIH's past policy that it is better to maximize the research scope of our competing research projects through full funding than to maximize the number of competing awards through additional downward negotiations.

TRAINING

Mr. Natcher. Your FY 1987 budget would cut the number of trainees being supported in research training programs from 10,623 supported in FY 1985 down to 9,258 in FY 1987. Does this represent a planned phaseout of training programs?

Dr. Wyngaarden. The FY 1987 budget for the National Research Service Award (NRSA) program does not represent any attempt to phase out the research training program. Fiscal constraints dictate some selective reductions in this area as in other NIH funding mechanisms. However, a strong program in research training will continue as a special feature of NIH extramural activities.

Mr. Natcher. What are your long-range plans for support of training?

Dr. Wyngaarden. The long-range plans for support of NRSA research training are to maintain support as near the level of 10,000 individuals per year as overall budget considerations allow.

Mr. Natcher. If we are going to support only 18,000 research project grants for the foreseeable future, should we continue to support 10,500 trainees each year as you recommended in your speech to the AAMC?

Dr. Wyngaarden. Even if we are going to support only 18,000 research grants for the foreseeable future, the NRSA program should be maintained near the 10,000 trainee per year level. This number is about 500 short of what has been recommended by the National Academy of Sciences personnel needs study published in September 1985.

It is noteworthy that NRSA funds support individuals who contribute to research funded via other mechanisms; e.g., research project grants, research contracts, and center grants. Therefore, it is important that we maintain a continuous supply of investigators entering the system.

SUPPORT PROVIDED THROUGH EXTRAMURAL PROGRAMS

Mr. Natcher. How many individuals in total do you estimate are being supported through NIH extramural programs?

Dr. Wyngaarden. We estimate that 60,000 to 65,000 individuals are supported through the NIH extramural programs.

NEW RESEARCH GRANT PROGRAMS

Mr. Natcher. You have recently instituted two new types of research grants. Please describe each of these new grants and explain their purposes.

Dr. Wyngaarden. On January 13, 1986, the Acting Assistant Secretary for Health approved two new types of research grants for implementation by the NIH beginning during the last half of the calendar year. These are the Method to Extend Research in Time (MERIT) and the First Independent Research Support and Transition (FIRST) awards.

The MERIT award provides long-term grant support to investigators whose research competence and productivity are distinctly superior and who are likely to continue to perform in a superior manner. This award will consist of conventional 5-year grants, followed by a 3- to 5-year competing renewal extension in those instances where the cognizant national advisory council/board and program staff determine that achievements during the first 4 years warrant that action. Review of a progress report and an abstract of the research plan (accompanied by a budget plan) for the extended period will determine if a particular award meets the criteria for an extended period of support.

The FIRST award provides a sufficient initial period of research support for newly independent investigators to develop their research capabilities and demonstrate the merit of their research ideas. These awards will generally be for 5 years with total direct costs for this period not to exceed $350,000. They offer the opportunity for newly independent investigators, whose initial research plans merit funding, an opportunity to demonstrate creativity, productivity, and further promise during their transition toward traditional types of research project grants.

Both MERIT and FIRST awards give the principal investigator authority to carry over unobligated balances from one budget period to the next. The FIRST award also permits an investigator to extend the final budget period one time for up to a year without additional funds unless otherwise restricted by a condition of the award.

Mr. Natcher. Given the shortage of research funds, does it make sense at this time to award grants for longer periods?

Dr. Wyngaarden. Both MERIT and FIRST awards represent an approach to efficiency and productivity that is entirely responsive to periods of shortage of research funds.

With regard to the MERIT award, the improved efficiency and productivity result from several factors: the decreased time required by the investigator to apply for other competitive renewal of his/her grant; the added stability that this type of award provides to the research environment of the investigator's institution; and the decreased effort and expense on the part of NIH administrative staff in terms of full-scale duplication of applications and their review. The feature of limited competition decreases this review activity considerably.

The FIRST award replaces the present New Investigator Research Award (NIRA), which usually is for a 3-year period and provides for maximum yearly support of only $35,000. By the time 18 months have expired on a NIRA award, the newly independent principal investigator must devote increasing time and effort to preparing a renewal application, often before he/she has had an opportunity to demonstrate the efficacy of the research plan of his/her capabilities to perform creative investigations. This circumstance can result in the loss to the biomedical research community of investigators who, given inadequate time to demonstrate their capabilities on their initial independent research effort, may be unable to compete successfully for renewed support. As in the case of the MERIT award, the longer period of support also decreases administrative costs of the review process at NIH.

The features of automatic carryover of unobligated funds (in both awards) and of optional extension of the final budget period of the FIRST award also impose fewer administrative burdens on the NIH and relieve the investigator from many activities and concerns that are not related directly to the research itself.

REDUCTION IN FULL-TIME EQUIVALENT POSITIONS

Mr. Natcher. You are proposing to support 12,649 full-time equivalent positions in FY 1986 and FY 1987, a reduction of 451 below the FY 1985 level. What are the comparable FTE figures for FY 1982, FY 1983, and FY 1984?

Dr. Wyngaarden. The comparable FTE figures are as follows: 1982 - 12,689; 1983 - 13,414; and 1984 - 13,661.

Mr. Natcher. How do you propose to achieve the FTE reduction proposed in the budget?

Dr. Wyngaarden. To achieve this FTE reduction, the NIH will re-evaluate the priorities of program resources, impose selective hiring restrictions, continue review of selected functions/services for possible contracting-out, and continue the elimination of the summer employment program.

Current estimates indicate that the proposed reduction would come from the following areas: 208 FTEs from the intramural research program; 60 FTEs from administrative staff and staff associated with managing the extramural program; 79 FTEs from central services such as police and fire protection, procurement, and maintenance services; and 104 FTEs from Cancer Control, the National Library of Medicine, and the Office of the Director.

Every effort will be made to minimize the impact on the research program and on patient care activities.

Mr. Natcher. Who decides how many FTEs will be allocated to HHS, the Public Health Service, and the NIH?

Dr. Wyngaarden. The Department receives a total FTE ceiling from OMB, the Public Health Service from the Department, and the NIH from the PHS in coordination with the Department.

STAFFING AT NIH

Mr. Natcher. What is the Administration's long-range plan for staffing at NIH?

Dr. Wyngaarden. At this time the Administration has provided FTE ceilings for 1986 and 1987. We have not received any FTE levels beyond these years.

Mr. Natcher. To what extent are you able to replace Federal employees by contracting-out?

Dr. Wyngaarden. NIH has always contracted for a portion of the services it requires and has provided the balance with internal staff. For example, 85 percent of renovation and alteration services are performed by contractors. Lately, because of the Administration's policy of looking to the private sector for commercially available goods and services, we have been shifting the mix to more contracting for several types of services. We now buy more media and make less in our own facility. We expect that eventually some services will be totally provided by the private sector, such as housekeeping.

We hope to control the pace of these conversions in order to protect current employees and avoid disruption of research support services. For example, our housekeeping function is being gradually converted to contract, building by building, with employees being relocated to vacancies in other buildings. In this way we are able to ensure the continuity of services that support the research scientists and provide protection to our service employees. We intend to continue this successful technique for the transition of services to the private sector in all areas where contract conversion is appropriate.

CLINICAL CENTER STAFFING

Mr. Natcher. Do you have a problem recruiting and retaining nurses to staff the Clinical Center?

Dr. Wyngaarden. First, the work for nurses at the Clinical Center deals with multiple research demands, complex patient care needs, and high numbers of acutely ill patients on most units. The work environment is a stressful one, with many chronically ill patients separated from traditional support structures, which intensifies the nursing need. On many units, nurses work additional hours of overtime when nurse/patient ratios are low.

Another factor that contributes to the problem of recruiting and retaining nurses at the Clinical Center is the Federal personnel system. The salary structure is not competitive with private or even other Federal pay scales, such as the system used by the Veterans Administration. In addition, there is no provision for special pay rates for extremely stressful work areas, no ability to give bonus payments for either recruitment or retention purposes, lack of comparability in employee benefits, lack of flexible part-time plans for weekend staffing, lack of benefits for part-time nurses, lack of on-call pay for nurses, and low differentials for working nights, evenings, and weekends.

Mr. Natcher. How many of the beds in the Clinical Center are you unable to use because of lack of staff?

Dr. Wyngaarden. Approximately 60 to 80 beds are unused because of lack of staff positions. It should be noted, however, that a delicate balance exists between available beds, nursing (and other) resources, and the acuity and complexity of patient care and research demands. Nursing and Clinical Center management are responsible for assuring that resources are adequately matched to patient care and research requirements. These two factors vary dramatically with the nature of the diagnosis, treatment, and protocol needs of patients. They vary with weekday, weekend, and month of year fluctuations as well. The nursing resources available to care for patients are finite and quantifiable. Therefore, the numbers and kinds of patients tend to fluctuate in accordance with available nursing staff. This means that at one time a unit may be 100-percent occupied by less acutely ill patients, whereas at another time it may be only 50-percent occupied with very intensively and acutely ill patients who individually demand more nursing time.

More predictable patient care requirements and more flexible nurse staffing would more adequately support a higher bed occupancy in the Clinical Center. The Nursing Department is presently working to achieve both goals.

RESEARCH PROJECT GRANTS

Mr. Natcher. Your justification shows that, if the proposed rescissions are approved, you will fund only 5,492 competing projects. We have received from the President a proposed change in the language of section 202 of the 1986 Appropriation Act. If this language is approved by Congress, but the proposed rescissions are not approved, how many competing projects will you fund in FY 1986?

Dr. Wyngaarden. If this were the case, we would probably propose to fund between 5,700 and 5,800 competing research project grants. However, this would require further discussions at NIH before a final decision could be made.

Mr. Natcher. The message from the President proposes bill language which would eliminate the requirement to fund at least 6,100 new and competing projects in FY 1986. The FY 1987 budget proposes language to require the NIH and the Alcohol, Drug Abuse, and Mental Health Administration to support no fewer than 19,400 research grants in FY 1987. Please explain the reasons for both of these proposals.

Dr. Wyngaarden. The proposals were developed as a result of the reduced levels of support possible in the FY 1986 revised estimate and as a means to facilitate the implementation of the new research project grant stabilization policy in FY 1987. Without the proposed new language, NIH would be required to support 6,100 competing grants in FY 1986. At the FY 1986 revised dollar level for research project grants, this would necessitate that NIH negotiate the average costs of competing grants downward from full study section recommended amounts by almost 15 percent. The proposed language for 1987 is to reflect the new policy for NIH, which is to stabilize the total number of grants at 18,000.

1987 BUDGET REQUEST LEVELS

Mr. Natcher. Please supply for the record a copy of your 1987 budget submission to the Public Health Service and the Department.

Dr. Wyngaarden. The following table shows by mechanism the NIH submission to the Public Health Service and the Department of Health and Human Services. The formal submission to the Department follows:

DHHS-National Institutes of Health

1987 BUDGET REQUESTS
(In thousands of dollars)

	NIH ESTIMATE TO PHS 1/		PHS ESTIMATE TO DHHS 1/	
Research Grants	No.	Amount	No.	Amount
Research Projects:				
Noncompeting	10745	$1,930,169	12994	$2,324,571
Admin. supp.	(459)	13,719	(406)	12,532
Competing	8500	1,392,310	6500	1,101,226
Subtot.,Competing	8500	1,392,310	6500	1,101,226
Subtotal, RPGs	19245	3,336,198	19494	3,438,329
Research Centers:				
Special/competing	422	437,363	343	343,439
GCRC	80	97,867	79	95,706
Biotech	58	37,550	54	33,365
LASPR	44	43,037	46	37,110
Gorgas	1	2,173	1	2,173
Subtotal, Centers	605	617,990	522	511,793
Other Research:				
Careers	1618	100,952	1384	83,562
Organ systems	1	1,042	1	1,042
Clinical education	69	7,000	51	5,303
Cooperative clinics	358	75,265	298	63,300
BRS	741	114,697	701	104,697
MBRS	89	44,298	81	41,000
Other	795	78,792	590	57,888
Subtotal, Other	3671	422,046	3106	356,792
Total,[illegible]	23521	4,376,234	23122	4,306,914
Training				
Individual	1608	43,654	1412	40,791
Institutional	8892	204,771	8588	191,341
Total, Training	10500	248,425	10000	232,132
Contracts	1544	509,287	1337	434,658
Intramural		681,082		658,994
RM&S		241,464		222,082
Control		102,939		70,244
Construction		84,349		40,349
Total, IRDs		6,243,780		5,965,373
Nat. Library of Medicine		76,675		71,131
Office of the Director		42,833		41,312
Buildings & Facilities		51,800		15,640
TOTAL NIH		6,415,088		6,093,456

1/ The base used for the development of these submissions was the 1986 President's Budget of $4,852,680.

Public
Health
Service

Preliminary Budget Submission to DHHS

Fiscal
Year
1987

National Institutes of Health

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

National Institutes of Health

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Department of Health and Human Services
Public Health Service
National Institutes of Health

1987 DHHS Budget Submission
Overview

Introduction

The National Institutes of Health (NIH) is the principal biomedical research agency of the Federal Government. Through the support and promotion of biomedical research, NIH seeks to improve the health of the American people by increasing the understanding of processes underlying human health, disability, and disease; advancing knowledge concerning the health effects of interactions between man and the environment; and developing methods of preventing, detecting, diagnosing, and treating disease. In the pursuit of this mission, NIH supports biomedical and behavioral research in this country and abroad, conducts research in its own laboratories, trains promising research scientists, and promotes the development and distribution of medical knowledge. Such research activities will determine much of the quality of health care for the future and reinforce the quality of health care currently available.

The uncertain status of the 1985 budget and its impact on the 1986 budget, the base year, adds complexities to the development of the preliminary budget for 1987. As of this date the Office of Management and Budget (OMB) and the Senate have reached a compromise on a level of 6,000 new and competing research project grants for 1986. This proposal could be further modified by House action. The levels submitted in this preliminary budget will, therefore, need to be adjusted when the 1985 and 1986 levels are resolved. In a departure from previous practice, this submission does not provide allocations by Institute because of the uncertainty in the base year; the budget estimates are provided in aggregate mechanism only.

1986 Budget Adjustments

The 1986 President's Budget has been adjusted to reflect the increased cost for research project grants as the result of the OMB and Senate compromise to support 6,000 competing research project grants in 1985 and 1986, the restoration of the proposed 5-percent pay cut in 1986, and the proposed budget amendments for expanded research on the acquired immune deficiency syndrome (AIDS) and on pertussis vaccine development. The additional funds requested in the budget amendments will enable NIH to take advantage of new opportunities resulting from recent scientific breakthroughs.

31-2

Of the $10,367,000 increase for AIDS, $4.6 million would be provided to NCI; $.6 million to NIDR; $.4 million to NINCDS and $4.7 million to NIAID. Some examples of research activities that would be supported are: conducting clinical trials with suramin and other drugs to determine their inhibitory effects against the virus; screening for other possible antiviral compounds; testing of candidate vaccine preparations; reconstituting the immune system through techniques such as bone marrow transplantation; and developing improved detection tests for AIDS. The budget amendment includes 52 FTEs.

Of the $2,287,000 increase for pertussis vaccine development, $1.6 million would be provided to NIAID and $.6 million to NICHD. Some examples of research activities that would be supported are: conducting safety and antigenicity studies of candidate vaccines in Sweden; phase I testing of four additional candidate vaccines; searching and planning for alternate study sites to perform additional efficacy trials for testing newly available vaccines; and developing animal models for assessing toxicity and potency of new vaccines. The budget amendment includes 4 FTEs.

1987 Budget Policy

The 1987 budget submission is organized by funding mechanism and contains three levels: OMB Target Level - $5,619.9 million and 13,028 FTEs; High Priority Level - $5,820.6 million and 13,191 FTEs; and Request Level - $6,093.5 million and 13,534 FTEs. The 1987 budget request is predicated on the revised 1986 budget as described in the previous section and will require updating once final decisions are made on funding policies and levels for 1985 and 1986.

OMB Target Level

The OMB Target Level of $5,619.9 million represents a $346.5 million increase, or 6.6 percent, over the revised 1986 budget.

At this level, support would be provided for 12,994 noncompeting research project grants at $2,212.3 million and 6,000 new and competing research project grants at $992.2 million. The average cost increase for noncompeting and new and competing research project grants provided at this level would be 4.2 percent over 1986. NIH estimates the average cost increases to be 9.5 and 7.2 percent for noncompeting and new and competing research project grants, respectively. Thus, the OMB Target Level would necessitate negotiations of approximately 4.8 percent in noncompeting below estimated commitments and 2.8 percent in new and competing below estimated study section recommended levels. Funding at this level would continue the freeze on indirect cost rates at the 1985 level.

Research centers, other research grants, R&D contracts, intramural research, cancer control, and construction would receive a 4.2 percent increase, in the aggregate, to offset the effects of inflation. Approximately 9,900 research trainees (FTTPs) would be supported with no increase over 1986 in stipend levels, tuition, or institutional allowance amounts.

Funds would be included for the implementation of several program and management initiatives: $12.1 million for NICHD's low birth weight prevention initiative, which is designed to reduce infant mortality and morbidity through improved obstetric and pediatric treatments; an additional $2.6 million over the proposed 1986 budget amendment for the pertussis vaccine development effort; $4.5 million for the establishment of a new personnel system of compensation within the Public Health Service to attract, retain, and motivate qualified doctoral-level scientists and engineers to work in Federal laboratories; and $1.5 million for upgrading telecommunications switching devices.

The building and facilities account would be funded at approximately $5 million to support the routine repair and improvements projects. There is no provision for the continuation of the Clinical Center Modernization project at this level.

High Priority Level

The High Priority Level of $5,820.6 million represents a $547.1 million increase, or 10.4 percent, over the revised 1986 budget.

This level would provide support: to fund the 12,994 noncompeting and the 6,000 new and competing research project grants at historical levels--reductions would be about 1 percent from the full direct costs of commitment for noncompeting grants and about 3 percent from study section recommended levels for new and competing grants; to provide for an increase in support of existing research centers; to provide for an increase in non-stipend costs in research training; and to continue the Clinical Center Modernization project. Full indirect costs on research grants would be provided at this level.

Enhancements at this level would include $32 million for intramural research to provide for an increase in centrally furnished services and supplies, FTEs and modest expansion for some high priority areas of research; and $2 million for the National Library of Medicine for the further development of the Intregrated Academic Information Management System (IAIMS), Medical Informatics Research, and the Unified Medical Language System project.

Request Level

The Request Level of $6,093.5 million represents a $819.9 million increase, or 15.5 percent, over the revised 1986 budget. This level of resources reflects the judgment as to how today's scientific opportunities could best be addressed. The long-term health of the biomedical research enterprise depends upon a continuing investment in the infrastructure and human capital upon which it is so dependent. This investment is essential if NIH is to continue its crucial role of maintaining the Nation's preeminent position of leadership in biomedical research.

The Request Level would support an additional 500 competing research project grants for a total of 6,500. This level represents an award rate of approximately 35 percent. In addition to the modest growth for competing research project grants, additional amounts would be provided to the other research mechanisms to ensure a more balanced program of activities so essential to the scientific enterprise.

Research training serves to replenish the Nation's corps of biomedical research investigators. It takes many years to develop high quality researchers and the level of training supported today determines our research capability in the future. Thus, the NIH continues to place high priority on research training. The Request Level would support a total of 10,000 trainees, compared to 9,891 in 1986 and the 1987 OMB Target Level. In addition to the increase provided at the High Priority Level, a 4.2 percent stipend increase would be provided within this level.

The request also includes approximately $40 million to begin to address the growing needs of the extramural community for the construction and renovation of laboratory research facilities.

Funds are also included for the implementation of the National Chimpanzee Management Plan to increase the availability of chimpanzees for biomedical research.

In addition, funds would be provided for several energy conservation projects and for the design of a multi-agency research building for use by NIH, FDA and ADAMHA, to be located on the NIH campus.

Other Issues

After several years' experience with Small Business Innovative Research (SBIR) grants, NIH is considering moving them from research project grants into a separate mechanism in the budget display. This approach would have several advantages: 1) better visibility for the program, 2) elimination of distortions in average cost figures and payline statistics for research project grants; and 3) better reflection of the fact that more than one mechanism is involved in SBIR. For informational purposes, the budget submission includes an alternative mechanism display that tentatively locates all SBIR awards, into a separate, distinct budget line item. This display, of course, reduces the number of new and competing research project grants but avoids confusion of the SBIR awards with the traditional R01 and P01 grants.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
National Institutes of Health

1987 ESTIMATE TO DHHS

(Dollars in thousands)

	1985 1/ Estimate	1986 2/ Estimate	1987 OMB Target Level	1987 High Priority Level	1987 Request Level
Research Project Grants	$2,786,999	$2,999,607	$3,217,016	$3,357,942	$3,438,329
Research Training	217,943	217,943	217,943	220,688	232,132
Other Research	1,366,621	1,293,698	1,396,623	1,412,623	1,525,325
Intramural Research	593,058	581,745	610,594	642,594	658,994
Cancer Control and Construction Programs	76,978	74,845	77,811	77,811	110,593
National Library of Medicine	54,762	54,152	57,173	59,173	71,131
Office of the Director	37,085	36,608	37,812	37,812	41,312
Buildings and Facilities	21,730	14,900	5,000	12,000	15,640
Central Services	(375,353)	(411,511)	(429,273)	(443,556)	(443,556)
Total	5,145,176	5,273,498	5,619,972	5,820,643	6,093,456

1/ Excludes $4,809 placed in reserve in accordance with Section 515 of the Treasury Postal Service Appropriations Act.
2/ Includes the effect of funding 6,000 competing research project grants in 1985 and 1986; $19,101 for restoration of 5% pay cut; $2,287 for pertussis initiative; and, $10,367 for AIDS research programs

DHHS - National Institutes of Health

1987 PRELIMINARY TO DHHS

Summary by Mechanism

(Dollars in thousands)

	FY 1985 1/		FY 1986 Revised 2/		1987 OMB Target Level		1987 High Priority Level		1987 Request Level	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Grants										
Research Projects:										
Noncompeting projects	12,172	$1,830,697	12,457	$2,035,363	12,994	$2,212,274	12,994	$2,324,571	12,994	$2,324,571
Administrative supplementals	(499)	18,665	(400)	12,027	(406)	12,532	(406)	12,532	(406)	12,532
Competing projects:										
One year competing	6,000	900,023	6,000	952,217	6,000	992,210	6,000	1,020,839	6,500	1,101,226
Three year competing	(118)	37,614	(118)	---	(118)	---	(118)	---	(118)	---
Subtotal competing	6,000	937,637	6,000	952,217	6,000	992,210	6,000	1,020,839	6,500	1,101,226
Subtotal, research projects	18,172	2,786,999	18,457	2,999,607	18,994	3,217,016	18,994	3,357,942	19,494	3,438,329
Research Centers:										
Specialized/comprehensive centers	328	306,196	312	289,953	330	320,457	330	329,723	343	343,439
General clinical research centers	76	82,675	72	77,254	76	84,739	76	88,733	79	95,706
Biotechonlogy resource grants	51	26,736	37	18,504	51	26,256	51	27,015	54	33,365
Lab. animal sciences & primate rsc.	44	29,663	33	24,681	44	33,913	44	34,894	46	37,110
Gorgas memorial institute	1	1,999	1	1,999	1	2,083	1	2,083	1	2,173
One yr. research centers	500	447,269	455	412,391	502	467,448	502	482,448	523	511,793
Two yr. research centers	(45)	34,875	(45)	---		---		---		---
Subtotal, Research Centers	500	482,144	455	412,391	502	467,448	502	482,448	523	511,793
Other Research:										
Research career programs	1,335	75,081	1,284	74,083	1,284	77,536	1,284	77,536	1,384	83,562
Cancer organ systems	1	1,000	1	1,000	1	1,000	1	1,000	1	1,042
Clinical education programs	53	5,000	51	5,000	51	5,210	51	5,210	51	5,210
Cooperative clinical research	303	53,579	291	53,777	264	56,036	264	56,036	298	63,393
Biomedical research support	701	96,335	701	96,335	701	99,381	701	100,381	701	104,697
Minority biomedical support	83	34,869	79	35,031	77	36,502	79	36,502	81	41,000
Other research related	526	42,786	519	38,213	519	39,818	519	39,818	590	57,888
Subtotal, other research	3,002	308,650	2,926	303,439	2,899	315,483	2,899	316,483	3,106	356,792
Total, Research Grants	21,674	3,577,793	21,838	3,715,437	22,395	3,999,947	22,395	4,156,873	23,123	4,306,914
Training										
Individual awards	1,458	37,890	1,397	36,275	1,397	36,275	1,397	36,275	1,412	38,019
Institutional awards	8,433	180,053	8,494	181,668	8,494	181,668	8,494	184,413	8,588	194,113
Total, Training	9,891	217,943	9,891	217,943	9,891	217,943	9,891	220,688	10,000	232,132
Research and Development Contracts	1,171	360,713	1,152	367,755	1,214	394,423	1,214	394,423	1,337	434,658
Intramural Research		583,058		581,745		610,594		642,594		658,994
Research Management and Support		215,114		210,113		219,269		219,269		222,082
Disease Control		63,878		61,745		64,160		64,160		70,244
Construction		13,100		13,100		13,651		13,651		40,349
Subtotal, IRD's		5,031,599		5,167,838		5,519,987		5,711,658		5,965,373
National Library of Medicine		54,762		54,152		57,173		59,173		71,131
Office of the Director		37,085		36,608		37,812		37,812		41,312
Buildings and Facilities		21,730		14,900		5,000		12,000		15,640
Total, NIH		5,145,176		5,273,498		5,619,972		5,820,643		6,093,456

1/ Excludes $4,809 placed in reserve in accordance with Section 515 of the Treasury Postal Service Appropriations Act.
2/ Includes the effect of funding 6,000 competing research project grants in 1985 and 1986; $19,101 for restoration of 5% pay cut; $2,287 for Pertussis initiative; and, $10,367 for AIDS research.

DRAFT

DHHS - National Institutes of Health

1987 PRELIMINARY TO DHHS

Summary by Mechanism with Separate SBIR

(Dollars in thousands)

DRAFT

	FY 1985 1/		FY 1986 Revised 2/		1987					
					OMB Target Level		High Priority Level		Request Level	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Grants										
Research Projects:										
Noncompeting projects	12,090	$1,818,389	12,347	$2,017,397	12,852	$2,188,105	12,854	$2,299,539	12,848	$2,298,492
Administrative supplementals	(499)	18,665	(400)	12,027	(406)	12,532	(406)	12,532	(406)	12,532
Competing projects:										
One year competing	5,754	863,100	5,792	919,143	5,814	961,449	5,814	988,980	6304	1,068,035
Three year competing	(118)	37,614	(118)	---	(118)	---	(118)	---	(118)	---
Subtotal competing	5,754	900,714	5,792	919,143	5,814	961,449	5,814	988,980	6,304	1,068,035
Subtotal, research projects	17,844	2,737,768	18,139	2,948,567	18,666	3,162,086	18,668	3,301,051	19,152	3,379,059
Research Centers:										
Specialized/comprehensive centers	328	306,196	312	289,953	330	320,457	330	329,723	343	343,439
General clinical research centers	76	82,675	72	77,254	76	84,739	76	88,733	79	95,706
Biotechonlogy resource grants	51	26,736	37	18,504	51	26,256	51	27,015	54	33,365
Lab. animal sciences & primate rsc.	44	29,663	33	24,681	44	33,913	44	34,894	46	37,110
Gorgas memorial institute	1	1,999	1	1,999	1	2,083	1	2,083	1	2,173
One yr. research centers	500	447,269	455	412,391	502	467,448	502	482,448	523	511,793
Two yr. research centers	(45)	34,875	(45)	---		---		---		---
Subtotal, Research Centers	500	482,144	455	412,391	502	467,448	502	482,448	523	511,793
Other Research:										
Research career programs	1,335	75,081	1,284	74,083	1,284	77,536	1,284	77,536	1,384	83,562
Cancer organ systems	1	1,000	1	1,000	1	1,000	1	1,000	1	1,042
Clinical education programs	53	5,000	51	5,000	51	5,210	51	5,210	51	5,210
Cooperative clinical research	303	53,579	291	53,777	264	56,036	264	56,036	298	63,393
Biomedical research support	701	96,335	701	96,335	701	99,381	701	100,381	701	104,697
Minority biomedical support	83	34,869	79	35,031	79	36,502	79	36,502	81	41,000
Other research related	526	42,786	519	38,213	519	39,818	519	39,818	590	57,888
Subtotal, other research	3,002	308,650	2,926	303,439	2,899	315,483	2,899	316,483	3,1[illegible]	356,792
Total, Research Grants	21,346	3,528,562	21,520	3,664,397	22,067	3,945,017	22,069	4,099,982	22,781	4,247,644
SBIR	328	49,231	318	51,040	320	54,930	326	56,091	342	59,270
Training										
Individual awards	1,458	37,890	1,397	36,275	1,397	36,275	1,397	36,275	1,412	38,019
Institutional awards	8,433	180,053	8,494	181,668	8,494	181,668	8,494	184,413	8,588	194,113
Total, Training	9,891	217,943	9,891	217,943	9,891	217,943	9,891	220,688	10,000	232,132
Research and Development Contracts	1,171	360,713	1,152	367,755	1,214	394,423	1,214	394,423	1,337	434,658
Intramural Research		583,858		581,745		610,394		642,394		658,974
Research Management and Support		215,114		210,113		219,269		219,269		222,082
Disease Control		63,078		61,745		64,160		64,160		70,264
Construction		13,100		13,100		13,651		13,651		40,349
Subtotal, BID's		5,031,599		5,167,838		5,519,787		5,711,658		5,965,373
National Library of Medicine		54,762		54,152		57,173		59,173		71,131
Office of the Director		37,085		36,600		37,812		37,812		41,312
Buildings and Facilities		21,730		14,900		5,000		12,000		15,640
Total, NIH		5,145,176		5,273,490		5,619,772		5,820,643		6,093,456

1/ Excludes $4,009 placed in reserve in accordance with Section 515 of the Treasury Postal Service Appropriations Act.

2/ Includes the effect of funding 6,000 competing research project grants in 1985 and 1986; $19,101 for restoration of 5% pay cut; $2,287 for Pertussis initiative; and, $10,367 for AIDS research.

FUNDING LEVEL SUMMARY

Department of Health and Human Services
Public Health Service - National Institutes of Health

Research Project Grants - 1301

Program Authorization: Titles II, III and IV of the Public Health Service Act

	Historical				FY 1987							
Resource Requirements	FY 1985		FY 1986		(1ax of 4)		(2b of 4)		(3s of 4)		(4d1 of 4)	
Budget Authority ($000)		$2,786,999		$2,999,607		$2,324,571		$3,217,016		$3,357,942		$3,438,329
Project Grants:												
Noncompeting..............	12172	1,830,697	12457	2,035,363	12994	2,324,571	12994	2,212,274	12994	2,324,571	12994	2,324,571
Admin. Supplementals.....	(499)	18,665	(400)	12,027		---	(406)	12,532	(406)	12,532	(406)	12,532
Competing:												
One yr. competing......	6000	900,023	6000	952,217	--	---	6000	992,210	6000	1,020,839	6500	1,101,226
Three yr. competing....	(118)	37,614	(118)	---	--	---	(118)	---	(118)	---	(118)	---
Subtotal, competing..	6000	937,637	6000	952,217	--	---	6000	992,210	6000	1,020,839	6500	1,101,226
Total	18172	2,786,999	18457	2,999,607	12994	2,324,571	18994	3,217,016	18994	3,357,942	19494	3,438,329

Research Project Grants

Explanation of Request

Goals/Purpose:

The mission of the National Institutes of Health (NIH) is to improve the health of the people by increasing our understanding of the processes underlying human health and by acquiring new knowledge to help prevent, detect, diagnose, and treat disease. In pursuing this mission, the NIH seeks to use research project grants:

- to maintain strong and steady support of the search for fundamental knowledge necessary to meet the full range of health problems;
- to apply this new knowledge to clinical practice;
- to integrate NIH health research with that conducted by other organizations in this country and abroad; and
- to provide adequate resources to sustain and enhance the research capability of the Nation's biomedical institutions.

Activity Description:

The NIH is the largest single source of support for biomedical research conducted in the universities, medical schools, dental schools, and research institutions of this Nation. Such support is awarded through the successful submission, review, and approval of grant applications. A major type of grant for research funding is the investigator-initiated research project grant. Such grants are the most effective means of supporting the innovative scientific inquiry necessary to build the knowledge base of the biomedical sciences. The subject matter of research project grants covers the entire biomedical continuum, from molecular and cellular investigations to studies of human beings in healthy and diseased states. Typically, NIH awards its traditional research project grants to support discrete, relatively modest-sized activities in areas that represent both the specific interests and competence of the principal investigators and the Institutes' identified program needs.

Some recent accomplishments brought about through research project grants include:

- A recent discovery shows that inheritable chromosomes in cultured cells of healthy individuals and within families contain "fragile sites" which are sensitive to breakage and also appear to be at the same breakpoints associated with lung cancers and leukemias. This important area of research holds promise for a major breakthrough in cancer prevention through the use of "fragile-site" analysis for population screening and cancer risk assessment.

- Research has perfected a noninvasive, simple measurement to rapidly identify infants with significant hemolytic disease, a disease characterized by the destruction of red blood cells and jaundice.

- Advances in molecular genetics are being used to determine the mechanisms of toxic chemical interactions with genes. By understanding how gene structure is altered by reactions with environment compounds, tests can be developed to predict toxic effects and to screen human populations for prior exposures to carcinogenic/mutagenic chemicals.

- A number of findings from diverse studies are showing a variety of nutritional influences on blood pressure regulation. Excess dietary sodium, for instance, is believed to be a central feature of essential hypertension in some "salt-sensitive" individuals, and low sodium diet helps lower blood pressure in hypertensives. In addition, high potassium diet is associated with low levels of blood pressure. There is also an association between low calcium intake and high blood pressure; evidence that magnesium and certain amino acids may influence blood pressure; and evidence that an interaction exists between metabolisms of carbohydrates and sodium. Other research further suggests a relationship between absolute fat content of diet and blood pressure regulation. It should now be possible to begin identifying specific mechanisms relating nutrition to blood pressure regulation and hypertension.

- Researchers have reported four monoclonal antibodies which are labeled Alzheimer neurofibrillary tangles. Further work with these monoclonal antibodies has lead to the development of quantitative assays for determining the relative amounts of antigen present in cerebrospinal fluid (CSF). The research indicates that there are significant differences between subjects with Alzheimer Disease (AD) and controls without neurological diseases. Further studies with these antibodies may prove to be very important because of their possible usefulness for a laboratory diagnostic test for AD.

- In certain diabetics, autoimmune mechanisms appear to be responsible for the illness. In such patients, immunosuppression with cyclosporine has been found by researchers to alleviate the disease by decreasing production of antibodies directed against the insulin producing cells of the pancreas. Thus, dependence on external sources of insulin may be reduced.

- Utilizing the normally inactive second strand of double-stranded DNA (referred to as the "antisense strand"), researchers have developed an effective method for selectively blocking the expression of specific genes. The approach used has the potential for allowing scientists to determine the role of many genes, the functions of which are not yet known, and may eventually permit physicians to "shut off" the expression of defective genes responsible for a wide range of inherited diseases.

- The discovery that an illicit synthesized variant of a "street drug" caused extreme Parkinsonism symptoms led scientists to identify the contaminant, MPTP, and to develop a new drug and animal models of the disease. Scientists are investigating inhibitors of MAO, a brain enzyme involved in MPTP toxicity, in animal models as a possible preventive approach. The MPTP research may lead to prevention of the disease as well as more effective, safer drug treatments.

- Recent discoveries in the molecular genetics of osteogenesis imperfecta have revealed four specific defects in collagen structure. Research project grants will continue to be supported to differentiate the effects of these defects, and to pursue their causes.

- Researchers have found that laser treatment can improve central vision in some patients who have experienced blockage of a retinal vein. This is an eye problem that affects many people who have blood pressure or diabetes. A clinical trial is continuing to explore the risks and benefits of laser treatment in people with the disorder.

1987 Request

The 1987 request incorporates the following funding policies:

- **The highest priority continues to be placed on funding new and competing research project grants. The preliminary submission would support 6,000 new and competing research project grants at the OMB Target and High Priority Levels, which is consistent with the Administration and Senate compromise for the 1986 budget. A total of 500 additional new and competing research project grants for a total of 6,500 would be provided at the Request Level.**

- The request also supports a total of 12,994 noncompeting research project grants.

- The direct costs requested for noncompeting and new and competing research project grants would require downward negotiations at the OMB Target Level. Full funding would be provided at the High Priority and Request Levels.

- Indirect cost rates would remain frozen at the 1985 rates at the OMB Target Level. At the High Priority and Request Levels, indirect cost would be funded at the level to which they would otherwise be expected to rise to in 1987, if the rates were not frozen in 1986.

The table on the following page summarizes the numbers and average costs of the research project grants at each 1987 level compared to 1985 and 1986:

Research Project Grants 1/

	1985 Estimate		1986 President's Budget Adjusted		1986 Revised Estimate	
	No.	Avg. Cost	No.	Avg. Cost	No.	Avg. Cost
Noncompeting..	12,172	$150,402	12,457	$160,500	12,457	$163,391
Admin. Suppl..	(499)	37,405	(400)	30,068	(400)	30,068
Competing.....	6,000	148,205	6,000	154,800	6,000	158,703
TOTAL......	18,172	159,480	18,457	163,210	18,457	162,519

	1987 Request							
	1ax of 4		2b of 4		3s of 4		4dl of 4	
	No.	Avg. Cost	No.	Avg. Cost	No.	Avg. Cost	No.	Avg. Cost
Noncompeting..	12,994	$178,896	12,994	$170,253	12,994	$178,896	12,994	$178,896
Admin. Suppl..	---	---	(406)	30,867	(406)	30,867	(406)	30,867
Competing.....	---	---	6,000	165,368	6,000	170,140	6,500	169,419
TOTAL......	12,994	178,896	18,994	169,370	18,994	176,790	19,494	175,717

1/ The 1987 average cost figures for new and competing grants are based on the Total Competing Requirements (TCR) Model. This model uses a linear statistical regression of 5 years of historical data encompassing the number and costs of grants approved by study section to estimate the current total competing requirements.

Two 1986 columns are shown for comparison purposes. The first 1986 column reflects the average cost assumptions used at the time the 1986 President's Budget was formulated. The second 1986 column reflects current average cost assumptions for 1986 that incorporate actual 1985 study section approvals to date into the five-year regression used to project 1986 and 1987.

The average costs contained in the submission still require some further refinement.

Package 1ax of 4 - This package would provide support for 12,994 noncompeting research project grants for $2,324.6 million. This estimate reflects full direct and indirect costs, less the routine discretionary adjustments inherent in the grants administration process. Historically, these routine adjustments have averaged 1 percent in noncompeting research project grants. This level of resources would provide an average cost increase of 9.5 percent over the 1986 revised budget.

Package 2b of 4 - This package totals $3,217.0 million. It would provide a net increase of $892.4 million over the previous level. Noncompeting research project grants estimate would be reduced by $112.3 million; $992.2 million would be provided for 6,000 new and competing research project grants; and $12.5 million would be provided for 406 administrative supplementals.

Noncompeting research project grants estimates were reduced in order to fund 6,000 competing research project grants and remain within the OMB Target Level. Noncompeting grants would be provided a 4.2 percent average cost increase over the 1986 average cost instead of the 9.5 percent increase required for the full funding. Downward negotiations of approximately 4.8 percent beyond the routine discretionary adjustments would be required. The indirect cost freeze policy included in the 1986 budget would be continued.

Competing research project grants also reflect a 4.2 percent average cost increase over the 1986 average cost. Downward negotiations of approximately 2.8 percent beyond the routine discretionary adjustments would be required. The indirect cost freeze policy included in the 1986 budget would be continued.

At this level of resources, projects would be initiated in such high priority areas as: investigations of Alzheimer disease; studies on the role of the immune system in allergic and immunologic diseases; nutrition research at the cellular and molecular level; molecular genetics; geriatric research; and research on sexually transmitted diseases.

Package 3s of 4 - This package totals $3,357.9 million and would provide an increase of $140.9 million to fund noncompeting commitments and 6,000 new and competing research project grants at full direct and indirect costs, less the routine discretionary adjustments inherent in the grants administration process. Historically, these routine adjustments have averaged about 1 percent in noncompeting research project grants and 3 percent in new and competing research project grants. This funding level is consistent with the policy of the 1984 and 1985 appropriations in which Congress determined that no arbitrary reductions should be made in the costs of grants other than normal technical adjustments. This same policy was incorporated by the Administration in the development of the 1986 budget.

In addition, indirect costs are funded at the levels to which they would otherwise be expected to rise to in 1987 if there were no freeze in 1986.

Package 4d1 of 4 - This package totals $3,438.3 million, and would provide an increase of $80.4 million to support an additional 500 new and competing research project grants for a total level of 6,500. This level of grants is consistent with the FY 1985 Appropriation and would support an award rate approximately 35 percent compared to 32 percent with 6,000 grants.

Additional grants at this level of effort would include projects such as: expansion of projects to assess the damaging effects of environmental factors, nutritional deficiencies, and drugs on retinal function; development of screening systems for ocular toxicity; research to accomplish genetic manipulations such as mapping, cloning and experimental insertion of normal genes; continuation and expansion of research on infectious particles and their role in degenerative brain diseases such as Alzheimer disease; and research on oral microbiology and immunology.

FUNDING LEVEL SUMMARY

Department of Health and Human Services
Public Health Service - National Institutes of Health

Other Research - 1303

Program Authorization: Titles II, III and IV, Public Health Service Act

	Historical				FY 1987									
Resource Requirements	FY 1985		FY 1986		(1a of 5)		(2s of 5)		(3d1 of 5)		(4d2 of 5)		(5d3 of 5)	
Budget Authority ($000)		$1,372,008		$1,293,698		$1,360,029		$1,385,423		$1,396,623		$1,412,623		$1,525,325
Full-time equivalent employment (workyears)...........		2294		2272		2272		2272		2272		2272		2347
Budgeted Positions..................		2151		2151		2151		2151		2151		2151		2151
Mechanism:	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Centers:														
Specialized/comprehensive......	328	306,196	312	289,953	328	319,057	328	319,057	330	320,457	330	329,723	343	343,439
General clinical research......	76	82,675	72	77,254	76	84,739	76	84,739	76	84,739	76	88,733	79	95,706
Biotechnology research.........	51	26,736	37	18,504	51	26,256	51	26,256	51	26,256	51	27,015	54	33,365
Lab animal science and primate research.............	44	29,663	33	24,681	44	33,913	44	33,913	44	33,913	44	34,894	46	37,110
Gorgas Memorial Institute......	1	1,999	1	1,999	1	2,083	1	2,083	1	2,083	1	2,083	1	2,173
Subtotal, one yr,rsch.cntrs..	500	447,269	455	412,391	500	466,048	500	466,048	502	467,448	502	482,448	523	511,793
Subtotal, two yr,rsch.cntrs..	(45)	34,875	(45)	---	(45)	---	(45)	---	(45)	---	(45)	---	(45)	---
Total, Research Centers....	500	482,144	455	412,391	500	466,048	500	466,048	502	467,448	502	482,448	523	511,793
Other Research														
Research career programs.......	1335	75,081	1284	74,083	1071	64,586	1284	77,536	1284	77,536	1284	77,536	1384	83,562
Cancer organ systems...........	1	1,000	1	1,000	0		1	1,000	1	1,000	1	1,000	1	1,042
Clinical education programs....	53	5,000	51	5,000	31	3,568	51	5,210	51	5,210	51	5,210	51	5,210
Cooperative clinical research..	303	53,579	291	53,777	264	56,036	264	56,036	264	56,036	264	56,036	298	63,393
Biomedical research support....	701	96,335	701	96,335	701	104,697	701	99,381	701	99,381	701	100,381	701	104,697
Minority biomedical support....	83	34,869	79	35,031	79	36,592	79	36,502	79	36,502	79	36,502	81	41,000
Other research related.........	526	42,786	519	38,213	335	35,652	519	39,518	519	39,818	519	39,818	590	57,888
Subtotal.....................	3002	308,650	2926	303,439	2481	301,131	2899	315,183	2899	315,483	2899	316,483	3106	356,792
Rsch. & Development Contracts.....	1171	360,713	1152	367,755	1151	374,081	1186	385,423	1214	394,423	1214	394,423	1337	434,658
Rsch. Management and Support.......		215,114		210,113		218,769		218,769		219,269		219,269		222,082
Total, Other Research......		1,366,621		1,293,698		1,360,029		1,385,423		1,396,623		1,412,623		1,525,325

Other Research

Explanation of Request

Goals/Purpose

Through the support and promotion of biomedical research, the National Institutes of Health (NIH) seeks to improve the health of the American people by: (1) increasing the understanding of processes underlying human health, disability, and disease; (2) advancing knowledge concerning the health effects of interactions between man and the environment; and (3) developing methods of preventing, detecting, diagnosing, and treating disease. To pursue this mission, the NIH effort in the other research category aims:

- To support multidisciplinary biomedical research which integrates basic research with applied research and transfer activities.
- To promote research activities in the areas of clinical applications with an emphasis on intervention, including prototype development and refinement of products, techniques, processes, methods, and practices.
- To develop and maintain the research resources needed by NIH-supported biomedical investigators for conducting their research.
- To support more contracted research which can be more easily targeted toward answering specific research problems.
- To provide support to enhance the career development of outstanding scientists with clear research potential, to improve the scope and quality of clinical teaching activities, and to encourage and promote the education of ethnic minorities in biomedical research.
- To include public participation in the setting of health research policies and principles that are responsive to public concerns.
- To provide scientific exchange opportunities which can translate research and development results into medical care practice in the United States and abroad.
- To provide the scientific and administrative management for the NIH research program.

Activity Description

The other research category covers a broad range of extramural biomedical research activities. Beside research project grants and training awards, the NIH provides research funding through several mechanisms: (1) research centers, which bring together the scientific and clinical expertise necessary for studying identifiable, investigative and clinical problems and for rapidly applying discoveries generated by basic research; (2) other research grants, including such programs as research career program awards, Minority Biomedical Research Support, Biomedical Research Support, and Clinical Education; (3) research and development contracts, which support more targeted research; and (4) research management and support, which provides scientific and administrative support for the NIH extramural and intramural research programs.

The following are examples of recent accomplishments achieved through the various other research mechanisms:

- A recent development in AIDS research is the demonstration that combination chemotherapy is well tolerated and can control the extensive Kaposi's Sarcoma often associated with this disease. It has also been shown that electron beam therapy can effectively control symptomatic Kaposi's Sarcoma confined to the skin in virtually all patients.

- The Surveillance, Epidemiology, and End Results (SEER) program has been used as a basis for a number of epidemiologic studies aimed at identifying possible factors in cancer causation. These studies have been carried out both within the National Cancer Institute and by other agencies. Examples are the national study of the relationship between artificial sweeteners and bladder cancer and the study of the relationship between the contraceptive pill and cancers of the breast, uterus and ovary.

- By encouraging close contact between clinical investigators and basic scientists, Specialized Centers of Research (SCOR) programs supported by NHLBI expedite clinical applications of basic science advances. For example, the first three centers in the United States to use tissue plasiminogen activator in the treatment of acute myocardial infarction were ischemic heart disease SCOR awardees. Moreover, the directions of basic science research tend to be responsive to the clinical needs in preventing, diagnosing, and treating SCOR subject diseases.

- Animal experiments at the Diabetes Research and Training Centers have contributed to the theory that altered white blood cell function plays an important role in insulin-dependent diabetes. Whole blood transfusions from non-diabetic animals to diabetic animals have had significant therapeutic effects.

- Significant scientific progress in research on different neuroprostheses has occurred this year. A single channel cochlear implant was recently licensed by the Food and Drug Administration. Scientists are actively working on more advanced speech processors to be used with both single and multichannel cochlear implants. This research may eventually provide significant aid to the profoundly deaf.

- The Clinical Investigator Development Awards (CIDA) program designed to train physician-scientists in research skills has been implemented.

- Investigators at an NIAID supported center have demonstrated that the use of antioxidants (metabisulfites) in the preservation of restaurant foods and in the manufacture of wines, beers, and many medications can provoke asthmatic reactions. Studies are underway to determine means to identify individuals at risk to such reactions.

- Bone marrow transplantation is being extensively used for treatment of congenitally immune deficient children and immune suppressed adults. NIAID-supported centers have overcome difficulties associated with this procedure by the use of monoclonal antibodies directed against the destructive cell elements contained in donor bone marrow.

- Investigators at a Burn and Trauma Research Center in Boston have continued to make significant improvements in the development of an "artificial skin" for covering severe burn wounds. The material they have developed speeds healing, reduces the threat of infection, and significantly reduces scar formation. A "Stage I" artificial skin developed by these same investigators has recently been approved by the FDA for clinical trials.

- Researchers working under a research center grant at Vanderbilt University have made significant advances in the study of mastocytosis, a sometimes fatal disease characterized by fainting episodes, flushing, tachycardia, diarrhea, and headaches. They have developed improved techniques for diagnosing this disease, discovering in the process that mastocytosis is more common than previously believed, and that the use of aspirin is an effective method of treatment.

- A disposable diaphragm which releases the spermicide, nonoxynol-9, for up to 24 hours has been successfully tested in animals by one NICHD contractor. An investigational new drug application has been approved by the FDA to conduct Phase I safety and preliminary efficacy studies in women.

- The continued utilization of fossil fuels has resulted in large releases of acidic combustion by-products into the atmosphere which causes the "acid rain" phenomenon. To study the health effects of these acid aerosols, the NIEHS has made available funds to study the human health consequences of inhalation of these ambient, oxidative pollutants.

- Programs for the development of physicians for both basic and clinical environmental health research have been initiated. The Physician Scientist Award supports clinically trained individuals to prepare for careers in basic biological and chemical research relating to chemical hazards in the environment. The Clinical Investigator Award supports physicians in research specialization relating to the recognition, diagnosis, prevention, and treatment of diseases caused by exposures to environmental hazards.

- The NIEHS arranged and coordinated the Third Task Force for Research Planning in Environmental Health Science.

- At one of the Alzheimer Disease Research Centers, it has been discovered that through nuclear magnetic resonance (NMR) imaging very early signs of small strokes or multi-infarct dementia can be detected and distinguished from Alzheimer disease. This will enable physicians to institute appropriate treatments, thus preventing further deterioration.

- Recent research applications of Nuclear Magnetic Resonance (NMR) spectroscopy at a DRP Biomedical Research Technology Center include the correlation of NMR-derived information on phosphate metabolism in the brains of newborn infants with learning disabilities such as dyslexia or retardation.

- Meharry Medical College investigators, supported by the Minority Biomedical Research Support Program, are attempting to identify various factors in the blood which are responsible for causing blood-vessel blockage in sickle-cell disease (SCD) patients. Preliminary studies show that specific venous-blood parameters vary consistently between the crisis and the non-crisis states of the SCD patients.

- The Fogarty International center sponsored the visit of a delegation of biomedical research scientists from the Romanian Academy of Medical Sciences to participate in the Third U.S.-Romania Workshop on Biomedical Research. The workshop, which was held under the auspices of the U.S.-Romania individual Health Scientist Exchange Program, was devoted to the topic of basic cancer research. During the delegation's visit, a memorandum of agreement between the National Cancer Institute and the Victor Babes Institute was made final.

1987 Request

The Preliminary Budget proposes to maintain the current level of activity and to provide additional resources for high priority clinical trials and prevention research as well as for expansion of all the various mechanisms in the other research category.

Package 1a of 5 - This package of $1,360.0 million represents the commitment base for other research and is an increase of $66.3 million over the revised 1986 budget.

At this level 500 research centers would be funded for a total of $466.0 million. The other research grants which include such mechanisms as research career program awards, cooperative clinical research and the biomedical research support awards would be supported at the commitment base level of $301.1 million. This package would support approximately 1,151 R&D contracts for a total of $374.1 million. The research management and support mechanism would receive $218.8 million, an increase of $8.7 million over the 1986 budget to provide administrative mandatories and inflation in non-pay items.

Package 2a of 5 - This package of $1,385.4 million would provide an increment of $25.4 million over the previous package. Of this increment, $14.1 million would be provided to other research grants and $11.3 million to research and development contracts in order to support current services in these 2 mechanisms.

Package 3d1 of 5 - This package of $1,396.6 million would provide an increase of $11.2 million over the previous package. These additional funds would provide increased programmatic support for the low birth weight prevention initiative of the National Institute of Child Health and Human Development (NICHD). Low birth weight is the major factor contributing to infant morbidity and mortality and the most important problem in maternal and child health today. Research efforts would be focused in the areas of premature labor and intrauterine retardation. The additional funds include $1.4 million for research centers, $.3 million for other research grants, $9.0 million for research and development contracts and $.5 million for research management and support. Other support for this initiative is included in the intramural research section.

Package 4d2 of 5 - This package of $1,412.6 million would provide an increase of $16.0 million over the previous package. Of this increment, $15.0 million would provide additional support to existing research centers and $1.0 million would restore support for the biomedical research support program reduced at the OMB Target Level.

Package 5d3 of 5 - This package of $1,525.3 million would provide an increment of $112.7 million over the previous package. This increment includes: $13.7 million and 13 specialized/comprehensive research centers; $7.0 million and 3 general clinical research centers; $6.4 million and 3 biomedical research technology centers; $2.2 million and 2 lab animal science centers; $.1 million for the Gorgas Memorial Institute; $40.3 million for 207 other research grants of which $6.0 millon would support 100 research career program awards $7.3 million would support 34 cooperative clinical research grants and $4.3 million would enhance the biomedical research support awards; $40.2 million and approximately 122 research and development contracts; and $2.8 million for the research management and support mechanism. Examples of additional programmatic activities reflected within this package are as follows:

- An initiative to establish centers for kidney and urologic research would be pursued. These centers would focus on a specific sector of end stage renal disease research.

- The NINCDS would fund additional centers in areas of scientific opportunity such as stroke, epilepsy, Parkinson's disease and spinal cord injury.

- An additional Asthma and Allergic Disease Center would be funded which would focus on topics such as adverse drug reactions.

- The biomedical research technology program would support 2 additional centers to address the need for advanced instrumentation and up-to-date technologies for research investigators. Special emphasis would be directed toward expanded biological applications of mass spectrometry, basic and clinical applications of nuclear magnetic resonance, and intermediate-voltage electron microscopy for cellular and molecular biology.

- Additional funds would be provided for the DRR Primate Research Centers for facility repairs, renovations, and replacement of major fixed equipment.

- The Research Career Program would provide support for 100 additional awards. These awards are designed to attract young physicians and scientists to research in basic and clinical studies of direct importance to the mission of the individual NIH Institutes. They provide mid-career support for scientists and physicians and are a key to developing vigorous research groups at medical schools.

- The clinical education program would place emphasis on introducing schools of public health and schools of nursing in a coordinated cancer teaching effort, especially in cancer prevention, nutrition and epidemiology. Through this assistance, more undergraduate students in professional schools and prebaccalaureate minority students would be engaged in individual activities designed to afford a broader understanding of cancer in its basic and clinical aspects. A continuing education program for health professionals would also be supported.

- Studies would continue on an animal model for tumor-associated weight loss. It is hoped that the factor released by the cancer to cause weight loss can be identified and characterized. A more complete understanding of the poor nutritional status of cachexia of many patients with cancer may uncover a way to either prevent or reverse this common complication of cancer.

- The Shared Instrumentation Program of DRR would be increased by $4.3 million to provide for additional support for maintenance and repair of instruments.

- The DRR would initiate an Animal Facilities Improvement Program to provide support for alterations and renovations of existing animal facilities to enable research institutions to meet current standards for the care and use of laboratory animals. This Program would be similar to one begun in 1985 with awards limited to $500,000 for alterations and renovations with a 50/50 matching of funds required by the institution.

- A National Chimpanzee management plan would be initiated at a cost of $8.9 million to increase the availability of chimpanzees for researchers. Awards would be made to five or six colonies who now own appropriate chimpanzee breeding stock and funds would be made available for animal maintenance, facility improvement, and research focused on neonatal mortality.

- Additional research to clarify the relation of dietary cholesterol and heart disease would be supported.

- In the area of biotechnology research, an application of recombinant DNA technology and monoclonal antibodies to cancer diagnosis and treatment would be supported. Monoclonal antibodies to human colon cancers, breast cancer and ovarian cancers have been used to detect recurrence of tumor after surgery, and should make it possible to reinitiate treatment before large amounts of recurrent tumor make this impossible.

- Additional contract funding would be used for an expanded program in contraceptive research. Areas of emphasis would include research on prevention of fertility by immunologic methods, development of contraceptive drug delivery systems, research on improvements in intrauterine contraception, and studies on the acceptability of currently marketed contraceptives.

- Studies would be designed to evaluate the influence of reductions in body weight through a moderate restriction of food intake on spontaneous tumor incidence. Also, the influence of this moderate dietary restriction on the sensitivity of NTP two-year carcinogenicity studies for detecting chemical carcinogens would be assessed.

- Approximately 75 additional FTEs are necessary to administer and monitor the higher level of research grants and contracts requested at this level.

FUNDING LEVEL SUMMARY

Department of Health and Human Services
Public Health Service - National Institutes of Health

Research Training - 1302

Program Authorization: Title IV, Part I, Public Health Service Act

Resource Requirements	Historical				FY 1987							
	FY 1985		FY 1986		(1a of 4)		(2c of 4)		(3e of 4)		(4d1 of 4)	
Budget Authority ($000)		$217,943		$217,943		$192,750		$217,943		$220,688		$232,132
Training:	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount	FT	Amount	FTE	Amount
Individual:												
Noncompeting............	898	23,223	911	23,515	854	23,216	854	23,216	854	23,216	854	22,994
Competing...............	560	14,667	486	12,760	--	---	543	13,059	543	13,059	558	15,025
Subtotal..............	1458	37,890	1397	36,275	854	23,216	1397	36,275	1397	36,275	1412	38,019
Institutional:												
Noncompeting............	5268	117,962	7489	156,294	7433	169,534	7433	158,976	7433	161,378	7433	168,007
Competing...............	3165	62,091	1005	25,374	--	---	1061	22,692	1061	23,035	1155	26,106
Subtotal..............	8433	180,053	8494	181,660	7433	169,534	8494	181,660	8494	184,413	8588	194,113
Total...............	9891	217,943	9891	217,943	8287	192,750	9891	217,943	9891	220,688	10000	232,132
Stipend levels:												
Predoctoral...........		$6,552		$6,552		$6,552		$6,552		$6,552		$6,827
Postdoctoral..........		$15,996 - 30,000		$15,996 - 30,000		$15,996 - 30,000		$15,996 - 30,000		$15,996 - 30,00		$16,668 - 31,260

Research Training

Explanation of Request

Goals/Purpose

The long-range goal of the NIH research training effort is to insure the necessary number of broadly trained scientists to carry out the Nation's biomedical and behavioral research programs. To this end, NIH seeks to support a critical mass of trainees learning, in the laboratory and at the bedside, to investigate health problems with applications to the prevention and treatment of disease. The NIH research training program provides the support that ensures a reliable continuum of creative, qualified scientists entering into research careers. These investigators are committed to advancing the state of the Nation's biomedical and behavioral research endeavors, fundamental to improving the Nation's health.

According to recent data, the average research career is extremely brief--only 6-10 years for principal investigators. A continuing study by the National Academy of Sciences (NAS) recognizes this atypical career pattern and acknowledges both the need for continuous replenishment of the profession and the propriety of partial Federal support for research training.

Specific objectives for the NIH research training program are:

- To maintain an optimal number of scientists in training for the conduct of national research objectives.

- To ensure that an appropriate number of physicians enter clinical research careers so that a reasonable proportion of M.D. to Ph.D. investigators is maintained and a rapid translation of basic science findings to the patient is facilitated.

- To attract and retain minority students with potential for research careers.

- To promote research training in priority areas such as clinical sciences, immunology, epidemiology, and biostatistics and computer sciences.

Activity Description

Research training serves to replenish the Nation's corps of biomedical research investigators. The National Research Service Awards (NRSA) program of the NIH supports, through institutional awards and individual fellowships, both basic and applied research training in the biomedical and behavioral sciences. Institutional awards provide the foundation for the manpower development effort by supporting the national capacity for excellent, up-to-date training in a variety of institutional settings. They enable NIH to aid institutions in maintaining vigorous and effective research training programs and, in particular, to support research training programs in areas of national need.

Individual fellowships complement the institutional award program. Fellowships support highly motivated scientists with specific training needs. The individual fellowship is requested directly from the NIH by an applicant who proposes a research project. Applicants must demonstrate the support of an acceptable sponsor and provide assurances that appropriate laboratory space will be available to them.

Decisions on the number of research trainees to be supported by NIH are based upon assessment of program needs and opportunities by the NIH Institutes, the NIH Director, recommendations of the National Academy of Sciences, and the availability of funds. The NIH Coordinating Committee on Manpower seeks to ensure that the individual Institutes, while providing for their own mission-oriented needs, address broader biomedical and behavioral problems in order to prevent either neglect of an area or duplication of effort. The NAS produces periodic reports on manpower needs, the most recent being the 1983 report, "Personnel Needs and Training for Biomedical and Behavioral Research." The areas of need identified by the NAS are consonant with those identified by the NIH, as are the projected number of trained scientists required to meet those needs.

Recent significant accomplishments in the NIH research training program include the following:

- In a report published in November 1984 (The Career Achievements of NIH Predoctoral Trainees and Fellows), the National Academy of Sciences (NAS) evaluated the impact of NIH's predoctoral training programs. The NAS concluded that, when looked at in comparison with other groups, NIH-supported trainees were more likely to: obtain their doctoral degrees; complete their training in shorter periods of time; apply for and receive grants-in-aid to support their research; publish a greater number of scientific articles; and have their publications cited by others in the bioscience literatures.

- The Medical Scientist Training Program (MSTP), which is administered by the NIGMS, is designed to address the long-term problem of a national shortage of biomedical researchers with clinical training by providing support to individuals seeking the combined M.D.-Ph.D. degree. A recent evaluation of this program indicates that it has continued to be a major success: Of the 351 MSTP graduates who are beyond residency training and who have entered their professional careers, 88 percent (308) are in university academic or biomedical research positions.

- The NIGMS Minority Access to Research Careers (MARC) Program has been remarkably successful in achieving its major objective; i.e., gaining, for highly qualified minority students, entrance into top-flight doctoral programs in the biomedical sciences. To date, approximately 85 percent of the graduates of the MARC Honors Undergraduate Research Training (HURT) component have gone on to either graduate or professional schools.

- Recent graduates of an NHLBI training program in cardiac cell membrane physiology have had their work published and presently hold junior faculty positions. Another NHLBI program in cardiac physiology has produced graduates who now either hold university appointments or are continuing their postdoctoral training.

- The NINCDS remains a vital funding source for research training in both the basic and clinical neurological and communicative sciences.

- The NIAID supports trainees in a variety of shortage areas such as immunology, clinical immunology, and basic microbiology.

- The NCI supports pre and postdoctoral research training in all of the sciences relevant to cancer.

- Ongoing comprehensive surveys in the areas of environmental toxicology and environmental epidemiology are documenting how current training programs are providing new researchers with the skills required for research careers in these fields.

- The NIA has initiated two new training awards: The Cooperative and Supplementary Training Awards for Research on Aging. These awards will help well established research training programs to increase the number of investigators they train for careers in aging.

1987 Request

In developing the following levels, NIH has placed special emphasis on providing stabilized and adequate support for research trainees. Overall, the NAS recommends that 12,595 trainees be supported through the NRSA program by NIH, HRSA, and ADAMHA in FY 1987. More specifically the NAS recommends that 725 trainees be supported under the Medical Scientist Training Program, a program designed to address the shortage of biomedical researchers with clinical training.

Package 1x of 4 - At this level of $192.8 million NIH would fund the commitment base level of 8,287 trainees; no new trainees would receive support.

Package 2c of 4 - At this level of $217.9 million NIH would fund 9,891 trainees, including 682 trainees in the Medical Scientist Training Program. As this is the same level of support included in the 1985 and 1986 budgets, no increases would be provided over these years in trainee stipends, tuition costs, or institutional allowances.

Package 3a of 4 - This level of $220.7 million would enable NIH to support 9,891 trainees. At this level, an increase for non-stipend would be supported. Specific areas of cost have risen much faster than the general level of inflation, and this trend is expected to continue.

Package 4d of 4 - This level of $232.1 million will enable NIH to support 10,000 research trainees, including approximately 690 trainees in the Medical Scientist Training Program. This number of trainees would ensure that a reliable continuum of creative, qualified scientists enter research careers and is more consistent with the NAS recommendation that approximately 10,500 trainees be supported by NIH in 1987. In addition to the increase provided for in the previous level, the request level would include a 4.2 percent stipend increase. Stipend levels were increased by Congress in the 1985 appropriations to make them more comparable with stipends paid by other Federal agencies and, for postdoctoral trainees, with salaries paid to house staff at U.S. teaching hospitals. To prevent an erosion in the real value of these stipends, it is necessary to budget for the impact of inflation in 1987. The following table shows NIH stipend levels for 1987 as well as those for 1985 and 1986.

Research Training
Stipend Amounts per Trainee

	FY 1985, FY 1986, and FY 1987 OMB Target/High Priority Levels	FY 1987 Request Level
Predoctoral..................	$ 6,552	$ 6,827
Postdoctoral		
Years of experience......		
0	15,996	16,668
1	17,004	17,718
2	21,996	22,920
3	23,004	23,970
4	24,000	25,008
5	26,004	27,096
6	27,996	29,171
7 or more	30,000	31,260

FUNDING LEVEL SUMMARY

Department of Health and Human Services
Public Health Service - National Institutes of Health

Intramural Research - 1304

Program Authorization: Titles II, III and IV, Public Health Service Act

	Historical		FY 1987			
Resource Requirements	FY 1985	FY 1986	(1sx of 4	(2d1 of 4)	(3d2 of 4)	(4d3 of 4)
Budget Authority ($000)	$583,058	$581,745	$609,694	$610,594	$642,594	$658,994
Full-time equivalent employment (workyears)...........	5024	5020	5020	5020	5145	5145
Budgeted Positions..................	4427	4427	4427	4427	4427	4427

Intramural Research

Explanation of Request

Goals/Purpose

The purpose of the intramural research program of the National Institutes of Health (NIH) is to conduct biomedical research to improve human well-being through greater understanding of the nature of life. To achieve this goal, the objectives of the intramural research program are:

- To conduct biomedical research to gain basic knowledge underlying the mechanisms of diseases.
- To support and encourage the translation of basic research results into health care delivery procedures through clinical investigations at the NIH Clinical Center.
- To pursue an intensified program of outpatient clinical studies at the Ambulatory Care Research Facility to further the goal of translating research protocols into clinical practice.
- To provide a group of scientific experts to advise the Institutes, the NIH, the PHS, and the DHHS on scientific matters.
- To provide research training in the latest biomedical techniques and approaches of intramural scientists to the cadre of young physicians and basic scientists who then apply what they have learned and train others upon their return to universities and medical schools.

Activity Description

Through the intramural research program, the NIH conducts basic and clinical research at its on-campus research facilities in Bethesda, Maryland, and at such off-campus locations as the Gerontology Research Center in Baltimore, Maryland; Research Triangle Park, North Carolina; the Rocky Mountain Laboratories in Hamilton, Montana; and Phoenix, Arizona. The fundamental research performed by intramural scientists provides the basis upon which advances in medical and dental care are built. An important byproduct of the research productivity is the cadre of young physicians and basic scientists who are trained in the techniques and approaches of the intramural scientists. One of the unique features of the NIH Intramural Research Program is the close proximity of many of its research laboratories to its 500-bed research hospital, the Clinical Center. This provides an opportunity for bridging the gap between basic and clinical science by carrying basic laboratory research to the bedside. With the completion of the Ambulatory Care Research Facility (ACRF) in FY 1982, the opportunities to translate basic research results into health care delivery systems utilizing outpatient programs have been greatly increased. Some recent accomplishments of the intramural program are as follows:

- The identification of the etiologic agent of AIDS (HTLV-III) by scientists in the Laboratory of Tumor Cell Biology, NCI represents an important scientific breakthrough. This discovery has permitted the immediate development of an effective transfusion screening test to protect the nation's blood supply, and will also allow development of an effective vaccine for high-risk individuals. In addition, this discovery will advance basic understanding of cancer as it relates to the human immune system.

- NIADDK scientists have patented an endothelial cell line which produces large quantities of Factor VIII:C, a clotting factor essential to treatment of hemophilia. Efforts to optimize the production and secretion of Factor VIII:C by these cells will be pursued.

- NICHD intramural scientists have recently isolated, purified and fully characterized the toxin of the pertussis organism (the bacteria which causes whooping cough), and have initiated field trials of the detoxified toxin which will form a much safer and more effective pertussis vaccine than any previously available.

- An NIA project used position emission tomography to study glucose utilization. The regional cerebral metabolic rate for glucose was examined in 40 healthy men between the ages of 21 and 83 years, under resting (unstimulated) conditions. Average hemispheric glucose utilization, and glucose utilization in 30 individual regions of the right and left hemispheres, were not related significantly to age. Because brain oxidative metabolism is not correlated with age in the absence of disease, compensatory mechanisms must exist in the healthy brain to overcome effects of cell loss and other age-related neurochemical and morphological declines.

- Scientists in the NIAID intramural research program have been able to produce a protein for use as a malaria vaccine after isolating and cloning the biologically active malaria sporozoite gene. The protein is dominant on the surface of the malaria sporozoite and is thought to be responsible for immunity. In tests conducted in animals, the protein was nontoxic and produced high levels of antibody. Human trials are now in progress.

- A graduate of the Pharmacology Research Associate Training (PRAT) Program received the ASPET Award for Experimental Therapeutics. Under the auspices of the PRAT Program sponsored by NIGMS, young scientists are selected each year for two years of postdoctoral research under the tutelage of preceptors in the laboratories of other NIH components. Since the program's inception in 1965, 90 percent of the 178 graduates have entered research careers.
- The NINCDS has continued its pioneering work on the study of neurogenetics of neurological disorders such as Gaucher's and other lipid storage diseases. Patients with Gaucher's disease are now being treated at the NIH Clinical Center with enzyme replacement therapy that is similar to the treatment diabetics receive to overcome insulin deficiency.
- The conventional view of coronary vasospasm is that angina is precipitated at rest as a result of a profound decrease in coronary artery flow caused by an occlusion of a large main coronary artery induced by spasm. Studies conducted by NHLBI have shown, however, that the small coronary arteries and arterioles, which are responsible for autoregulation of vascular resistance, may also be implicated. Some patients developing angina during a trial pacing to increase the heart rate, with or without the administration of the vasoconstrictor drug ergonovine, showed abnormal blood flow patterns associated with myocardial ischemia. Subsequent studies using quantitative coronary angiography demonstrated no significant narrowing of the large coronary vessels in response to ergonovine.
- NIEHS epidemiologists have studied the potential role of toxic exposures during pregnancy and early childhood on subsequent cancer risk in the adult offspring. Smoking was chosen as an exposure of interest because it was regarded as common enough possibly to produce a measurable effect. This exploratory study compared cancer patients and controls with regard to the smoking habits of their parents. There was a fifty-percent increase in overall cancer risk among persons who were exposed to smoking during childhood.
- Investigators in the NEI have obtained new information concerning oxidation within the eye. These findings should provide a basis for the development of drugs that can block or slow cataract development.

1987 Request

The budget request of $658.9 million proposes to maintain the current level of activity in intramural research and to provide for expansions in selected high priority areas.

Package 1ex of 4 - This level provides $609.7 million which represents the current services level for intramural activities. This represents about a $27.9 million or 4.8 percent increase over 1986 and would provide amounts needed for administrative mandatory increases, such as within-grade salary increases, Federal Telecommunications System cost increases, and utility rate increases, and for offsetting the effects of inflation on basic laboratory supplies and equipment as well as hospital supplies necessary to maintain ongoing basic and clinical research. Included also is the establishment of a personnel system of compensation for scientists.

Package 2d1 of 4 - The 610.6 million requested at this level includes $.9 million for the intramural part of the NICHD's low-birth-weight prevention initiative.

Package 3d2 of 4 - An increment of $32.0 million, for a total of $642.6 million would provide an increase in centrally furnished services and supplies, FTEs and a modest expansion for several priority areas of research. These program increases are proposed within the intramural research mechanism rather than in extramural mechanisms due to the availability of the necessary equipment and expertise at NIH. To attempt these efforts under the grant or contract mechanisms would not be as feasible or as cost-effective. Some of the studies conducted intramurally--for example, those involving positron emission tomography technology --are unique. Moreover, the NIH provides exceptional opportunities for consultation and collaboration among outstanding scientists from a wide variety of disciplines.

At this level, the additional resources for intramural research would enhance such areas of research as:

- Establishment of an interdisciplinary interactive exploratory vaccine development program that would closely interact with the private sector to produce vaccines.
- Additional research on gene-transfer mediated uses for heritable genetic disorders.
- Efforts to develop an AIDS vaccine based upon the studies in cell biology that are currently being carried out from which a retrovirus has been identified as the causative AIDS agent.

- Studies of insulin receptor binding and activation related to insulin resistance in diabetic patients.

- Expanded emphasis in the use of magnetic resonance imaging (MRI) in the study of serious neurological diseases and disorders such as Alzheimer disease.

- Studies of biochemical and genetic defects in retinitis pigmeutosa and other herditary retinal degenerative diseases, using new molecular biology techniques.

- Efforts to increase understanding of the role of certain oncogenes and their interaction with other genetic targets in neoplastic formation.

- A new initiative in geriatric research studies will be started.

- Approximately 125 FTEs would be restored at this level to accomplish these initiatives. Even with this FTE restoration, staffing levels would still be below the 1984 levels.

Package 4d3 of 4 - The request at this level is $658.9 million. The additional $16.4 million provided for intramural research at this level includes such activities as:

- Expansion of cardiovascular research as it relates to the elderly.

- Expanded research on the regulatory role of cell receptors for hormones, growth factors, antigens, neurotransmitters and drugs which promises to open up new opportunities for therapeutic intervention in many receptor-mediated disorders.

- Studies of critical mediator interleukin-1 as a rate limiting factor in lung cancer.

- Expansion of AIDS, CNS implantation studies, and Parkinson's disease research.

- The addition of more women to the Baltimore Longitudinal Study on Aging so that their numbers will be comparable to those of current male participants.

- Establishment of a new section in the Epidemiology and Oral Disease Prevention Program to collect and utilize data and information developed in other programs to accelerate improvements in oral health.

- Expanded basic research on immunologic disorders such as AIDS, systemic lupus erythematosus, and asthma.

- Expanded studies on aging-related maculopathy and other retinal degenerations.

- An additional 200 FTEs would be provided at this level to partially restore the intramural program to the 1984 staffing levels and to carry out the initiatives described above.

Department of Health and Human Services
Public Health Service - National Institutes of Health

Disease Control and Construction Program - 1305

Program Authorization: Title IV, Part A, Public Health Service Act

	Historical				FY 1987					
Resource Requirements	FY 1985		FY 1986		(1x of 3)		(2s of 3)		(3dl of 3)	
Budget Authority ($000)		$76,978		$74,845		$55,353		$77,811		$110,593
Full-time equivalent employment (workyears)...		111		110		110		110		130
Budgeted Positions........		95		95		95		95		95
	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount	FTE	Amount
Mechanisms:										
Cancer Control............	111	63,878	110	61,745	110	51,353	110	64,160	130	70,244
Construction Programs.....	--	13,100	--	13,100	--	4,000	--	13,651	--	40,349
Total..................	111	76,978	110	74,845	110	55,353	110	77,811	130	110,593

Disease Control and Construction

Explanation of Request

Goals/Purpose

Cancer Control: The NCI Cancer Control Program involves multifaceted research activities aimed at identifying research results that can be most effective in reducing cancer incidence, morbidity and mortality through prevention, early detection and improved cancer patient management. In effect, cancer control is the bridge between the basic and clinical research programs of the NCI and their application in the health care system. NCI has set a goal to reduce cancer mortality rates of today by 50 percent by the year 2000. The Control Program will play a major role in the attainment of this goal.

NCI Construction: The NCI Construction Program provides support to upgrade, modernize, renovate and develop cancer research facilities in order to fully comply with NCI and Department of Health and Human Services research safety standards.

The long-range objectives of the NCI Construction Program include: modernization of biohazard containment facilities; upgrading research animal facilities; the renovation of older clinical laboratories to permit the use of the latest technological advances; and the provision of additional cancer facilities at cancer research institutions.

NHLBI Construction: The NHLBI Construction Program provides grant support for the improvement, renovation, and establishment of research facilities relevant to contemporary biomedical sciences in organizations with substantial ongoing research activities in heart, lung, and blood diseases.

NEI Construction: Grants are awarded under the National Eye Institute Construction Grant Program for constructing or renovating physical facilities dedicated to eye research. The objective of this program is to increase the availability and improve the quality of vision research facilities.

DRR Construction: In order to address the growing problem of deteriorating and obsolete health research facilities, the NIH proposes a program designed to assist the research community in replacing outmoded facilities, including facilities for dealing with toxic wastes, for laboratory animals, and for major renovation and repair of inferior facilities. The program will be aimed towards relieving overcrowding and accommodating changing research requirements. This activity would require authorizing legislation.

Activity Description

Cancer Control: The Cancer Control Program has three major program activity areas, each supporting a group of cancer control strategies or approaches: Prevention, Centers and Community Oncology and Cancer Control Science.

The Prevention Program includes activities in chemoprevention, nutrition and screening/detection. The Prevention Program also serves as the focal point for all diet and cancer activities across the NCI. Screening and detection activities include research on the effectiveness of screening modalities for all cancer sites, especially breast, colon and cervix cancers, and the development and implementation of methodologies to track progress in screening and detection across the United States.

The Centers and Community Oncology Program includes activities in rehabilitation, continuing care and community oncology research as well as research on strategies to ensure comprehensive treatment procedures for all Americans. This area is the focus for development, application and dissemination of knowledge and technology related to cancer patient management. The Community Oncology Program and the Cooperative Outreach Program are cancer control efforts linking community-based physicians with cancer centers and clinical cooperative groups. Under these programs, local physicians participate in clinical trials which are sponsored by a cancer center or clinical cooperative group. The programs are based on the premise that participation in clinical research protocols will stimulate diffusion of high-quality medical care for all patients treated in the community by rapidly transferring new knowledge and therapies to the communities where most cancer patients are diagnosed and treated.

The Cancer Control Science Program is responsible for research on the health promotion sciences, for developing and evaluating strategies to implement cancer control and for developing a cadre of professionals trained to initiate and apply the results of cancer control research. Coordination and implementation of the Smoking, Tobacco and Cancer Program, a broad-based intervention research program, is also the responsibility of the Cancer Control Science Program. This program also tracks and evaluates progress in cancer control, identifying areas of the United States with particular cancer control needs and identifying ways of reducing cancer deaths in these areas throughout the country.

Studies targeted for support include:

- Plans to identify, develop, implement and evaluate cancer communications research projects targeted to specific audiences utilizing the resources of the Cancer Communications System (CCS). These research projects shall include innovative ways to reach specific target groups with cancer information and an assessment of its impact of their knowledge, attitudes and/or practices.

- State and local health agencies will demonstrate the feasibility and impact of the public health structure's contribution to a major decrease in cancer mortality by the year 2000. A program will be instituted to provide technical assistance through scientific consultation, program reviews, staff training and information exchange to State and local health agencies for organizing implementation of the year 2000 objectives. This program will ensure that health agencies wanting to develop cancer control programs have direct and rapid access to scientific expertise and information programs of the National Cancer Institute.

- A small grant program will be initiated to stimulate State and local health agencies to develop and/or adapt databases for cancer control program planning, modeling, development, and evaluation. This program is designed to ensure that existing tumor registries are utilized for cancer control purposes, as well as the usual epidemiologic purpose.

- A large, multi-study, multi-disciplinary center of research excellence, the Cancer Control Research Units (CCRU), will continue to conduct high-priority intervention research aimed at significant population effects on reducing cancer mortality by the year 2000. The second generation of CCRU grantees, reviewed in FY 1986, will implement their new research programs.

- Within selected geographic communities, plans are to develop, implement and pilot test interventions to: 1) stimulate and sustain increased utilization of mammography and breast palpation among women fifty years of age and older and their health care providers; and 2) upgrade the quality of these detection technologies.

NCI Construction: Areas of emphasis include:

- renovation of clinical laboratories to reflect new cancer research technologies and diagnostic measures;
- renovation of basic research laboratories to upgrade biohazard containment facilities; and
- renovation of animal facilities to meet mandatory DHHS standards for animal care.

NHLBI Construction: Areas of emphasis would include:

- alterations or renovations of existing physical facilities, primary laboratories.
- development or expansion of research facilities that will serve several research projects on a shared basis.

NEI Construction: Areas of emphasis include:

- development or expansion of a clinical research facility; and
- integration of basic and clinical research laboratories.

DRR Construction: Areas of emphasis include:

- renovation and/or construction of animal facilities;
- construction of toxic waste disposal facilities; and
- modernization or replacement of existing research facilities.

Accomplishments

Cancer Control:

- Consolidation and analyses of the Breast Cancer Detection Demonstration Program (BCDDP) data are continuing. The BCDDP reinforces data from previous studies that mammography and physical examination of the breast in women over 50 can have an appreciable effect on reducing mortality by approximately 30 percent. Furthermore, long-term follow-up of 65,000 of the women who participated in the breast cancer screening project has continued at a follow-up rate of more than 97 percent. It is anticipated that the information from this study will add significantly to information on the natural history of breast cancer and on the impact of screening for early detection.

Construction:

- The NCI Construction Program provides funding for the modernization, upgrading and renovation of existing facilities as well as new construction. The predominant amount of funds are utilized to renovate and upgrade existing facilities for basic and clinical activities. Additional support is provided for recombinant DNA technologies and renovation of buildings containing research animals to meet DHHS standards. The construction program generates matching funds from the private sector which greatly exceed the Federal government commitment to the total cost for the renovations or construction. Its objectives are to provide modern and safe facilities at cancer research centers for the accomplishment of basic and applied cancer research involving hazardous chemicals, viral agents and genetic materials. Usually, these materials have major unknown properties which require specialized hoods, containment and personnel protection.

1987 Request

Package 1x of 3 - This level of $51.3 million represents the commitment base for cancer control activities. The amount budgeted is $10.4 million below the 1986 budget. Ongoing studies would continue and no new initiatives would be pursued. This level also provides a total of $4.0 million for the NCI construction program.

Package 2s of 3 - Cancer Control: This level provides a total of $64.2 million for cancer control activities. This represents an increase of $12.8 million over the previous level and $2.4 million over the 1986 budget. Ongoing studies would be continued at the current services level. Efforts at this level also would include the initiation of a new program to address the significant differential in survival between certain minority populations (e.g., blacks) and the population as a whole.

Construction: This level would provides a total of $13.7 million for the extramural construction programs of the NCI, NHLBI, and the NEI. This is a 4.2 percent increase over the 1986 budget. Approximately $6.8 million would be for the Cancer Construction Program for the upgrading and renovation of existing cancer facilities. The NHLBI and the NEI construction programs would be funded at about $3.4 million each.

Package 3d1 of 3 - Cancer Control: This level of support would increase funding for cancer control activities by $6 million for a total of $70.2 million. Twenty (20) additional full-time equivalent (FTE) positions would also be provided. The research program to identify and correct the causes of avoidable cancer mortality (deaths that occur despite the existance of effective technology for their prevention, detection, and treatment) would be expanded. In addition, intervention studies in progress would be expanded to include pharmacokinetic studies of beta-carotene, studies of the effect of dietary fat on hormonal variation and fecal mutagens, additional studies on the toxicity of new chemopreventive agents in humans, and analysis of biological specimens in clinical trial participants for selected micronutrients.

Construction: This level would provide a total of $40.3 million for the NIH extramural construction programs. This is an increase of $26.7 million over the previous level. Over the past decade, growing concern has been expressed over the deterioration of research facilities in the nation's biomedical research institutions, and previous studies have pointed to some very serious problems. The enhancement described below would enable NIH to begin to address more fully these problems.

At this level, the NCI Construction Program would be funded at $12 million, a $5.2 million increase over the previous level. This increase would enable NCI to support a portion of the approved but unfunded applications that will carry-over from 1986. The construction programs of the NHLBI and the NEI would each be funded for a total of $4 million, an increase of $.6 million over the previous level.

This level would also allow the initiation of the DRR sponsored Facility Construction Program for a total of $20 million. These funds, provided on a matching basis of 2 dollars Federal per 1 dollar institutional, would build or renovate about 15 average sized medical facilities. This activity would require legislation providing a general extramural construction authority--that is, an authority not limited to specific categorical disease areas.

FUNDING LEVEL SUMMARY

Department of Health and Human Services
Public Health Service - National Institutes of Health

National Library of Medicine: 75-0807-0-1-550
1351

Program Authorization: Title III, Section 301 and Parts I and J of the Public Health Service Act
(Legislation for Part J is pending)

	HISTORICAL				1987			
Resource Requirements	FY 1985		FY 1986		(1x of 5)		(2x of 5)	
Budget Authority ($000)............		$54,408		$54,152		$54,900		$56,173
Full-time equivalent employment (workyears)............		527		521		521		521
Budgeted Positions.................		495		495		495		495
Mechanisms:	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Extramural - Grants								
Noncompeting......................	49	$3,899	68	$8,398	70	$9,084	70	$9,084
Competing.........................	64	6,041	13	1,542	---	---	22	1,273
Subtotal, Grants................	113	9,940	81	9,940	70	9,084	92	10,957
Extramural - Contracts								
Noncompeting......................	7	2,300	7	2,300	7	2,397	7	2,397
Competing.........................	---	---	---	---	---	---	---	---
Subtotal, Contracts.............	7	2,300	7	2,300	77	2,397	7	2,397
Total, Extramural...............		12,240		12,240		11,481		12,754
Intramural........................		36,490		36,276		37,574		37,574
Library Operations...............		(24,621)		(24,448)		(25,371)		(25,371)
Lister Hill Center...............		(8,521)		(8,490)		(8,766)		(8,766)
Toxicology Information...........		(3,348)		(3,338)		(3,437)		(3,437)
Research Management and Support...........................		5,678		5,636		5,845		5,845
Total..............................		54,408		54,152		54,900		56,173

	1987					
Resource Requirements	(3d1 of 5)		(4d2 of 5)		(5d3 of 5)	
Budget Authority ($000)............		$57,173		$59,173		$71,131
Full-time equivalent employment (workyears)............		521		521		553
Budgeted Positions................		495		495		495
Mechanisms:	**No.**	**Amount**	**No.**	**Amount**	**No.**	**Amount**
Extramural - Grants						
Noncompeting......................	70	$9,084	70	$9,084	70	$9,084
Competing.........................	25	1,873	31	2,873	91	10,548
Subtotal, Grants................	95	10,957	101	11,957	161	19,632
Extramural- Contracts						
Noncompeting......................	7	2,397	7	2,397	7	2,600
Competing.........................	—	—	—	—	—	—
Subtotal, Contracts.............	7	2,397	7	2,397	7	2,600
Total, Extramural..............		13,354		14,354		22,232
Intramural........................		37,974		38,974		42,964
Library Operations..............		(25,771)		(25,771)		(26,736)
Lister Hill Center..............		(8,766)		(9,766)		(12,750)
Toxicology Information..........		(3,437)		(3,437)		(3,478)
Research Management and Support........................		5,845		5,845		5,935
Total..........................		57,173		59,173		71,131

Goals/Purpose

The National Library of Medicine's purpose is to assist the advancement of medical related sciences, and to aid the dissemination and exchange of scientific and other information important to the progress of medicine and to the public health. Like any organization, in order for the Library to continue to achieve its goals, NLM also engages in research and development activities to improve the dissemination of biomedical information by applying the latest computer and communications technologies.

Activity Description

Extramural Programs

The extramural programs of the NLM are authorized by Section 301, Part I, and Part J (Medical Library Assistance) of the Public Health Service Act. These programs make possible a range of unique extramural programs of grants and contracts for better management, dissemination, and use of medical knowledge. NLM sponsors basic research and research training in Medical Informatics, in the management and delivery of information by way of modern health science libraries and library networks, and in the synthesis and interpretation of biomedical literature. The NLM grant and contract extramural programs complement each other in achieving these goals, and represent the only programs focusing on information issues that concern the entire health professional community.

o Research grants support fundamental investigations regarding the generation, organization, and utilization of health knowledge, with particular attention to the implications of advancing computer and communications technologies. NLM offers the principal support for Medical Informatics, an emerging discipline concerned with applying the latest advances in computer technology and information science to information processing, to improve patient care, medical education, and to support new research. Investigations have included:

  - Techniques for convenient bibliographic retrieval from large computerized databases, thereby permitting physicians and nurses to search the literature without a specially trained intermediary.

  - Better understanding of information structure as revealed by linguistic analysis of medical records and reports, thereby enabling improvement in the organization of medical knowledge.

  - New ways of adapting knowledge to computerized clinical problem-solving and decision aids. This work includes better understanding of the role of knowledge in medical judgment.

  - Development of computerized expert knowledge systems with which human users can consult interactively, in the same way that physicians now consult with their colleagues.

o Training grants support the training of talented younger persons who seek careers in health computer science research. The curricula are mutidisciplinary - involving medicine, the cognitive sciences, information science, and computer science. The emphasis at each training site is the opportunity for work in advanced information science research.

o The Integrated Academic Information Management Systems (IAIMS) programs, stimulated by an NLM-supported study by the Association of American Medical Colleges (AAMC), will use computer and communications technologies to bring together into one system the myriad sources of information now widely scattered throughout a major health science center. A typical scenario envisions the health professional, with a small desk top terminal, having rapid and easy access to a variety of computerized files--calling up patient records, ordering laboratory tests and reviewing their results, examining the professional literature, searching remote files such as a tumor registry in another state, consulting clinical decision-making systems, monitoring the progress of students, and communicating with his colleagues. Presently, research at seven different institutions has been supported by NLM for Phase I (planning). Phase II (development) awards are scheduled for late in FY 1985.

o Resource grants have funded a wide variety of projects to improve hospital and academic health-science library resources at the local level. More than 1,000 health care institutions have participated and received grant funds in this program. There also is a trend of more support to smaller hospitals, especially with consortia grants, thereby providing cost-effective information resources and services to health personnel at remote locations. The rapid advances in communications and computer technologies do not lessen but rather increase the need for the availability of local resources.

o The Regional Medical Library (RML) Network comprises 7 Regional Libraries, 100 Resource Libraries in academic medical centers, and some 3,000 libraries in hospitals and other health-related institutions. The RML network has been remarkably successful in expanding national access to NLM's online system, training personnel in basic library management, fostering the development of consortia and developing and implementing a regional automated document delivery system. To date, more than 15 million books and journals have been loaned and 10 million computer searches have been provided for health professionals.

- Publication grants have encouraged the writing and publishing of scholarly works, such as critical reviews and monographs in special areas of health research and practice. This program fulfills a need to provide low-cost, time-limited support for important publications in the health sciences that are not commercially profitable.

- Through the Medical Informatics program, NLM supports basic, investigator-initiated research on fundamental knowledge issues. These concern the extraction, organization, retrieval, and utilization of knowledge, involving methodologies such as artificial intelligence-related computer sciences, computational linguistics, medical decision science, cognitive psychology, bioethical issues and related information-oriented fields.

Library Operations

In FY 1984 186,000 items were acquired for the NLM collection; more than 358,000 requests were received for books and journals from on-site users and libraries throughout the U.S.; 87,000 reference questions were answered; 26,000 patrons made on-site use of the facility; 17,500 monographs and serials were cataloged; and more than 306,000 articles were indexed. These records were both published in printed form and added to the MEDLARS database to make them available for rapid search and retrieval.

Online searching of the MEDLARS databases was begun in 1971 and has provided rapid and convenient access to the world's medical literature for the health-science community. Currently, 20 different online databases are contained in the MEDLARS family. MEDLINE is the largest and most frequently used. Also available are specialized databases including several which are cancer-related and toxicology-related.

Lister Hill National Center for Biomedical Communications

The Lister Hill Center is the NLM's intramural research and development component, responsible for exploring the application of advances made in the fields of computer and communications technology to health information handling, processing and transfer problems, and medical education. In pursuit of this goal the LHNCBC has undertaken a program of studies to exploit the computer as a intellectual tool to enhance the availability of biomedical information. Current areas of research being conducted include:

- In FY 1985, the NLM has begun a program to address a most fundamental problem in medical informatics: the lack of unified standard medical vocabulary. For decades a major fundamental impediment to widespread adoption of a computer-based information system in medicine has been the absence of standard vocabulary, terminology, definitions, and criteria for recording the results of biomedical research, the events of clinical patient care, and the managerial and business transactions of hospitals. Working with the American Medical Association, university investigators in academic departments, health professional associations, and federal collaborators, NLM plans to coordinate a program to create a unified medical language system. This program would be guided by an advisory committee whose members include these groups and also insurance industry and relevant governmental agencies. The development of a unified medical language system is an important step in enhancing medical communications and should assist in the common goal of developing more cost effective national health care system.

- Recent advances in optical disc technology have resulted in higher quality pictorial/graphic imagery. LHNCBC plans to further explore applications of computer assisted instruction in medical education using the optical videodisc to create a series of computer-based simulations of the clinical encounter. An effective instructional program on radiology has been produced.

- A program of studies on human factors (such as man-machine interaction) in biomedical information transfer. This program will optimize the effectiveness and acceptance of new technologies to structure and automate biomedical information by the health science community.

- Examination of methodologies for electronically organizing machine-readable databases to increase the productivity of the indexing and cataloging activities. This research will help in establishing methods for processing literature currently not indexed or cataloged because of cost and other resource limitations.

- The LHNCBC has completed its first phase of a program in electronic document storage and retrieval (EDSR) using optical videodisc technology with the design and development of an experimental prototype system. This system will be used to conduct experiments in document capture, storage, retrieval and display. The long-term goal of the program is to introduce new technology to help the Library preserve the content of deteriorating literature.

Toxicology Information Program

The Toxicology Information Program (TIP) was established at NLM to provide national access to information on toxicology. The objectives of TIP are to: create computerized databases in the area of toxicology, pharmacology, and environmental health, and to provide toxicology information products and services to the scientific community.

- The computerized databases and specialized information services provided by NLM are an important link in the National Toxicology Program and other interagency collaborative efforts to improve the healthfulness of our environment.
- The TIP has received support under the "Superfund Act" to enhance and expand its existing online databases such as TOXLINE, CHEMLINE and the Toxicology Data Bank (TDB) to include more information on hazardous waste products likely to occur in waste dumps or in chemical accidents.
- The Library's Toxicology Information Program is developing a microprocessor-based workstation that could be used immediately to retrieve information by emergency response teams at the site of a chemical spill or accident. A prototype model of such a workstation is now being tested at NLM and at Oak Ridge National Laboratory.

1987 Request

In 1987, NLM will maintain its commitment to providing basic library services to the biomedical community. Emphasis will be placed on continuing to build and preserve our extensive collection of substantive biomedical literature and to provide access to that collection.

Package 1x of 5 - This package would provide the commitment base level of $54.9 million.

The extramural program would support 70 noncompeting grants in the Medical Library Assistance and Medical Informatics programs.

The intramural program, comprised of both services and research, would receive sufficient funds to cover mandatory increases, including a 4.2% inflation factor. At this budget level, NLM would maintain the provision of basic library and information services to the biomedical community; MEDLARS III, NLM's third generation computerized system for automating labor intensive internal library functions such as ordering, receiving, and cataloging; the Lister Hill Center's efforts in research and development program to explore the application of advances made in the fields of computer and communications technology to health information handling, processing and transfer problems; and the Toxicology Information Program.

Research Management and Support would receive funds to cover mandatory increases.

Package 2s of 5 - This package would provide $56.2 million, an increase of $1.3 million over the commitment base. This increase would support 22 competing grants in the Medical Library Assistance and Medical Informatics programs.

Package 3d1 of 5 - This package would provide $57.2 million, an increase of $1.0 million over the previous package of which $.6 million would support the enhancement of the Medical Informatics program and $.4 million would support the expanded activities in library operations due to growing volume of publications.

Package 4d2 of 5 - This package would provide $59.2 million, a $2.0 million increase over the previous package. Extramural programs would receive an additional $1.0 million for IAIMS development and for Medical Informatics research. The intramural program would also be provided an increment of $1.0 million to permit initial developmental efforts on the Unified Medical Language System project.

Package 5d3 of 5 - This package would provide $71.1 million, an increase of $11.9 million over the previous package. This increment would be provided to improve the nation's health through improved biomedical information services. In the IAIMS Program, which has generated much interest in the Congress and the nation's biomedical community, the development of prototype systems would be accelerated. A comprehensive Centers of Excellence in Medical Informatics program would be initiated. These centers would encompass training of skilled investigators, career development programs, core research, and departmental development in order to provide a stable research environment for research projects in Medical Informatics. In addition, this increase would provide for additional FTE's to significantly expand the Library's collaborative effort to create a Unified Medical Language System. Funds would also be provided to implement NLM's newly developed formal plan to preserve its collection of over 3 million items; to utilize the latest in computer and communication technologies such as optical disk storage and retrieval; additional FTEs, in order to keep up with the growing demand and need for increased and improved biomedical information services. The total FTE increase in this level would be 32.

FUNDING LEVEL SUMMARY

Department of Health and Human Services
Public Health Service - National Institutes of Health

Office of the Director: 75-0846-01-550

1354

	Historical		1987	
Resource Requirements	FY 1985	FY 1986	(1sx of 2)	(2dl of 2)
Budget Authority ($000)	$36,903	$36,608	$37,812	$41,312
Full-time equivalent employment (workyears):	536	516	516	532
Budgeted Positions	501	501	501	501

Explanation of Request

Goals/Purpose

The mission of the Office of the Director is to develop overall research policy for the intramural and extramural programs of the National Institutes of Health (NIH), coordinate research initiatives and programs that span two or more Institutes or divisions, and provide effective administration of essential centralized activities. Major objectives to be accomplished are the following:

- Maintain liaison within and outside the Federal government in matters relating to science policy, research administration, training in the research sciences, and communications in biomedicine.

- Direct the development and coordination of policies and procedures relating to the various extramural award mechanisms and provide a coordinated approach to the analysis and direction of the research training program and other trans-NIH activities.

- Establish overall research policy for the NIH intramural program.

- Participate in the establishment of policies pertaining to clinical research conducted or supported by NIH.

- Provide a focus for the assessment of health care technology and its effective transfer into the health care system.

- Carry out Congressionally mandated responsibilities such as the development and implementation of regulations for the protection of human subjects from research risks, as well as implementation of Executive Branch priorities in animal welfare and equal employment opportunity programs.

- Provide for the organization, direction, and coordination of NIH financial and personnel management, management analysis, investigative functions, and communications.

Activity Description

For reasons of efficiency and economy in operations, funds for the overall direction and administration of the National Institutes of Health and for the centralized provision of a number of very essential support services are provided through the appropriation to the Office of the Director. Chief among the component offices is the Immediate Office of the Director, which includes the principal associates of the Director and staff officers who provide advice and assistance in the administration and coordination of the intramural and extramural research programs of the Bureaus, Institutes and Divisions. Other offices provide leadership in such areas as equal opportunity, program planning and evaluation, disease prevention, medical applications of research, public and scientific communication, protection from research risks, management analysis and review, contract and grant administration and financial and personnel management.

Among the recent accomplishments of the Office of the Director are the following:

- An emphasis was placed on implementing new Congressional directives for Academic Research Enhancement Awards and Centers for Research in Minority Institutions. These and other established efforts, such as the Extramural Associates Program, were aimed at encouraging the participation of minority and other under-represented groups of scientists and institutions in NIH research programs. Related to these initiatives were staff efforts designed to provide appropriate technical assistance to non-traditional awardees such as small or minority schools and small business.

- Considerable effort was devoted to the implementation of the Small Business Innovation Research Program and the development of guidance for use by the potential applicants and the administering NIH program staff. This program, legislated under the Small Business Innovation Development Act, is intended to stimulate technological innovation and to use small businesses to meet the Federal R&D needs. NIH made 200 Phase I awards under the program totalling $9.7 million in 1984, and 46 Phase II awards totaling $11.2 million.

- As part of the NIH's ongoing efforts in the area of technology assessment and transfer, Consensus Development Conferences were held in the past year on osteogenic sarcomas, blood cholesterol and heart disease, traveler's diarrhea, obesity, anesthesia and sedation in the dental office, electroconvulsive therapy in psychiatry, and breast cancer. A major evaluation of the impact of selected conferences on medical practice is continuing in FY 1985 with final results expected by Spring 1986.

- The Office of the Director continued and increased its involvement in the development of policies and regulations for the protection of human research subjects and the care and use of laboratory animals. In cooperation with the Food and Drug Administration, the NIH continued to conduct educational workshops throughout the Nation in order to educate Institutional Review Boards, research investigators and administrators who are required to comply with HHS human subject regulations. In addition, an assurance program designed to bring Cooperative Oncology Group members and affiliates throughout the U.S. and foreign countries into full compliance with human subject regulations was developed and implemented.

- A working group on AIDS has continued to disseminate information relevant to NIH research efforts on AIDS. The working group, which is composed of Institute and OD staff, coordinates the preparation of all briefing material for congressional hearings, drafts press releases, prepares questions and answers for press briefings, collects budgetary information on AIDS research, and maintains a monthly monitoring system for all extramural expenditures on AIDS.

1987 Request

Package 1sx of 2 - This package for the Office of the Director would provide the commitment base level of $37.8 million. This amount would support the 1986 level of effort by providing for administrative mandatory increases such as within-grades, and FTS cost increase and inflation for non-pay items. The Academic Research Enhancement Award and the Research Centers at Minority Institutions would be provided, $10.4 million which includes a $.4 million increase over the 1986 level.

Package 2dl of 2 - The request level for the Office of the Director is $41.3 million, an increase of $3.5 million over the previous level. This funding increment includes an additional $3 million over the previous level for the Academic Research Enhancement Award and the Research Centers at Minority Institutions programs. These resources would permit additional institutions to participate in the programs. The request level also includes $.5 million for policy-related analyses and support services and 16 additional FTEs.

FUNDING LEVEL SUMMARY

Department of Health and Human Services
Public Health Service - National Institutes of Health

Buildings and Facilities: 75-0838-0-1-552

1356

Program Authorization: Title III, Public Health Service Act

	Historical		1987			
Resource Requirements	FY 1985	FY 1986	(1sx of 4)	(2d1 of 4)	(3d2 of 4)	4d3 of 4
Budget Authority ($000)	$21,730	$14,900	$5,000	$12,000	$13,000	$15,640

Explanation of Request

Goals/Purpose

The long-range goal of the NIH Buildings and Facilities program provides for the construction, improvement and major repair of clinical and laboratory buildings and supporting facilities essential to the conduct of the mission of the National Institutes of Health. Buildings and facilities covered under this appropriation include those at the main NIH Reservation, Bethesda, Maryland; the NIH Animal Center, Poolesville, Maryland; the Research Triangle Park, North Carolina; the Rocky Mountain Laboratory, Hamilton, Montana; the Gerontology Research Facility, Baltimore, Maryland; the Primate Facility, Perrine, Florida; and other NIH field stations.

Activity Description

The Buildings and Facilities appropriation responds to two major needs of the Federal biomedical research endeavor: the design and construction of new facilities for NIH research programs; and, the continuing repair and improvement of existing facilities or those under design or construction intended for support services to the research enterprise.

Construction of facilities for the National Institutes of Health began with the initiating legislation for Building 1 in June 1936. Over the next 49 years, 60 additional buildings were added to the Bethesda Reservation, providing more than 6 million gross square feet of space. The growth of science and corresponding support needs resulted in the addition of a number of facilities geographically distinct from the Bethesda campus.

The most recent addition to the real property holdings of the NIH is the Convent of the Sisters of the Visitation of Washington and the surrounding 11-acres at the northwest edge of the Bethesda campus. This is the only parcel of land contiguous to the NIH campus that is not already heavily developed. Currently the building and site are being developed jointly by the Howard Hughes Medical Institute and NIH under a cooperative program for a training and education center for medical students interested in pursuing careers in the research sciences.

Major facilities that have recently been constructed include the Ambulatory Care Research Facility (ACRF) in Bethesda and facilities for the National Institute of Environmental Health Sciences located at Research Triangle Park, North Carolina. Other projects which are under construction or have recently been completed include: modernization of the Clinical Center; the Radiation Oncology Facility; the Lister Hill National Center for Biomedical Communications; various elements of the master utilities system; an addition to the central refrigeration plant; renovation to the National Library of Medicine; the rehabilitation of older laboratory buildings; the cyclotron facility; and the expansion of radioactive waste area.

Major repairs and improvements of the plant facilities include the following: fire and safety protection improvements; improvements or replacement of elevators; replacement of roofs; repairs to roads, sidewalks and parking areas; provision of accommodations for the handicapped; energy conservation improvements; and modification of space to meet changed use requirements. Program related repair and improvements include the renovation to animal space in Building 14B; renovation of research space modules; modernization of the NIH centralized computer services activity; alterations of existing space to accommodate new laboratory and clinical programs; and modest renovations to the Convent.

1987 Request

Package 1sx of 4 - This package would provide $5.0 million for the Repairs and Improvements program, which applies to the physical plants at Bethesda, Poolesville, and Baltimore, Maryland; Research Triangle Park, North Carolina; Hamilton, Montana; Perrine, Florida; and other field stations for which NIH has the property-holding responsibility. Program related repairs and improvements are required to accommodate changes in the direction of research efforts. Projects supported with these funds are typically small and unanticipated to the extent that lead time is not sufficient to request funds during the regular budget cycle.

Package 2d1 of 4 - This package would provide $7.0 million for the Clinical Center Modernization program. Since the original planning and construction of the Clinical Center over 30 years ago, great advances have been made in American medicine. Yet, over these years, the Center has undergone only modest alterations, generally to satisfy unique program developments or equipment requirements. Extensive alterations at the Clinical Center are necessary to upgrade patient care and medical support spaces in order to remove functional obsolescence and repair physical deterioration; to satisfy the latest code requirements for the handicapped, for environmental health, and for the safety of the patients and the staff; and to integrate the activities in the Clinical Center with their functional counterparts in the new Ambulatory Care Research Facility completed in fiscal year 1982. We anticipate that the Clinical Center modernization will cost $81 million, based on 1987 dollars, and will be completed in 1993.

Adequate lead time and careful phasing of these projects must be ensured in order to minimize the impact on patients and research endeavors, as well as to synchronize individual projects with the ACRF schedule. The 1987 request would fund the activities in the ninth year of the project. These include renovation to patient care units to accommodate modern procedures and equipment and to correct obsolescence in nursing stations, medical support systems, and utilities.

Package 3d2 of 4 - This package would provide $1.0 million for several Energy Conservation projects. The Frederick Cancer Research Center provides specialized research space for research efforts of several Institutes. The reason for improvements to the Frederick Cancer Research Center (FCRC) is to improve the energy efficiency of existing buildings. Many of the facilities are very old and lack energy efficient construction such as insulation, thermal windows, and HVAC systems without heat recovery. In some cases program changes of the facility have resulted in the possible use of recirculated air, but due to current designs, the systems are not equiped to permit this.

A survey was conducted to identify energy conservation opportunities. Opportunities identified include shutdown of air systems in spaces that are unoccupied, reduction of lighting, resetting of air supply temperatures, recovery of heat from exhaust air, etc. By completing these improvements approximately 7,360,000 KWH would be saved annually at an initial cost of approximately $900,000--a savings of approximately $350,000 per year on utility bills and a payback in 2.6 years.

Package 4d3 of 4 - This package includes $2.6 million for the design of Building 49. The construction of Building 49 on the Bethesda Campus is intended to consolidate and provide improved space for several basic research programs of the NIH, FDA, and ADAMHA. The new research facility would provide 21,600 net square feet of space for NIH programs, 51,000 new square feet for FDA programs, and 45,000 net square feet for ADAMHA programs:

- The NIH space will provide for the return of the Campus of basic intramural research programs currently housed in the Park Building in Rockville, Maryland. The Park Building is a converted office facility which causes severe constraints on the research programs housed there.

- The FDA portion of the building will be utilized by the Center for Drugs and Biologics, which currently occupies nearby Building 29 and 29A. It will provide FDA with additional, required animal research space, and will house the bulk of its research and test development effort related to new drug evaluation.

- The ADAMHA portion will be utilized by NIMH programs currently located in the William A. White Building on the grounds of St. Elizabeths Hospital. That facility is scheduled to be transferred to the District of Columbia with the Hospital complex. It is also an obsolete facility which would require major expenditures if retained for NIMH research activities.

As a preliminary estimate, $57.1 million would be required in the future for construction. Approximately $3 million more would be required to construct a new multi-level parking facility to accommodate the surface parking lost with construction of the research facility.

FUNDING LEVEL SUMMARY

Department of Health and Human Services
Public Health Service - National Institutes of Health

Central Services: 75-3966-0-4-552/75-4554-0-552

1355

Program Authorization: (Management Fund: 42 USC 291, Service and Supply Fund: 42 USC 2331)

	Historical		1987	
Resource Requirements	FY 1985	FY 1986	(1sx of 2)	(2dl of 2)
Budget Authority ($000)	$375,353 [1]	$411,511 [1]	$429,273 [1]	$443,556 [1]
Full-time equivalent employment (workyears)	4,615	4,574	4,589	4,627
Budgeted Positions	4,503	4,503	4,503	4,541

[1] Dollar levels are included in the Institutes' budget estimates.

Explanation of Request

Goals/Purpose

The NIH Central Services provides the specialized services to the NIH Community that support the mission of the NIH intramural and extramural research programs. The goals are:

- To provide staff resources in formulating policies and procedures relating to the NIH extramural biomedical research programs and to provide initial scientific and technical review of all PHS research and training grant applications.

- To provide inpatient and ambulatory care services in an efficient and economical manner in order to maintain the high quality of clinical research at the Clinical Center (CC) and at the Ambulatory Care Research Facility (ACRF).

- To provide engineering, architectural, craft, and labor services required for the operation and maintenance of the NIH facilities as well as the planning of plant modernizations, program alterations, and improvements.

- To investigate new areas of research in computer sciences, mathematics, physical, and life sciences as they relate to the support of biomedical research and to provide a complete range of computer and data processing services.

- To provide scientific, technical and collaborative bioengineering services and products to support and further the intramural research programs at NIH as well as services to assure NIH compliance with various health, environmental control and safety requirements.

- To provide a centralized program of administrative and technical services in support of biomedical research, patient care, administrative management, and plant operations.

Activity Description

The NIH Central Services are comprised of those organizations designed to provide numerous specialized materials and support services to the NIH Community. These services include the following areas: grant review and approval, clinical investigative and inpatient/ambulatory care services, computer processing, research services, safety and occupational health, and administrative and engineeing services. NIH Central Services are financed through the NIH Management Fund and the NIH Service and Supply Fund. Major accomplishments during the past year include the following:

- Collaborative biomedical designing produced a series of flexible three - dimensional human heart models to demonstrate anatomical relationships and variations of idiopathic hypertrophic subatomic stenosis for medical students and patient education.

- New catheter technology was further developed to provide proven or potential solutions to a variety of problems such as negotiating small tortuous vessels, steering, insertion retrograde to blood flow, sampling and mixing.

- Initiatives in the area of diagnostic technology are continuing with particular emphasis being placed on collaborative programs in Positron Emission Tomography (PET) and Magnetic Resonance imaging.

- Further progress was made in the management of clinical data through the hospital's information management system.

- The Computer Systems laboratory has explored the use of Local Area Networks and the transmission of medical information and images and has implemented a network using Ethernet within the Division of Computer Research and Technology.

- The Division of Safety provided a comprehensive radiation safety program for approximately 4,700 persons at NIH to ensure the radiatin safety of personnel and the protection of the environment.

- Further progress was made in the implementation of a data communications network that will integrate the grant application receipt, processing, review and award procedures.

- Innovative techniques to improve engineering planning and facility maintenance were implemented concurrent with a restructuring of the Division of Engineering Services that was undertaken to effect economics while maintaining an efficient streamlined operation.

1987 Request

In 1987, the Central Services budget proposals reflect the commitment of those activities to provide the NIH research programs with services that are efficient, economical, and fully supportive of the NIH mission.

Package 1ex of 2 - This level would provide $429.3 million and would enable the NIH Central Services to provide essential support services to NIH's intramural and extramural research programs. These services include collaborative scientific, technical and bioengineering services; central scientific and computational data processing services; clinical investigative and patient care services; review of research grant applications for scientific merit; engineering and craft services to operate and maintain the various NIH buildings and facilities; environmental and employee health services; and administrative services, such as housekeeping, protection and security, supplies, and procurement. This package would maintain the existing level of services in support of NIH research efforts and programs and would include an additional 15 FTEs for the Financial and Administrative Integrated Management System (FAIMS).

Package 2d1 of 2 - This level would provide $443.6 million, an increase of $14.3 million and 38 FTE's over the target level to maintain a comprehensive and broad - based program of research support services to the NIH BIDs. Specifically, additional FTE's and related funds are requested to support the following activities:

Expanded collaborative clinical research: $4.6 million and 25 FTE's would provide essential support for a number of new or expanded Institute clinical research protocols as well as those clinical and scientific programs already under way. The NIH Clinical Center and the adjacent Ambulatory Care Research Facility (ACRF), support clinical protocols by providing a full range of patient care and basic hospital services, direct participation in collaborative research efforts with specific Institutes, specialized expertise and personnel state of the art diagnostic equipment, and centralized medical facilities. Specifically: Funding is required to support an increase in hospital supplies concomitant with the higher numbers of very sick patients that will be admitted to the Clinical Center. AIDS research and a significant expansion of the pediatric oncology program offer but two examples of new protocols, that generate high intensity care and thus require a higher volume of supplies per hospitalized patient.

Funds are requested to purchase a magnetic resonance imaging scanner (MRI) to meet the increased demands of the Institutes for MRI scanning. The Radiology Department of the Clinical Center currently has only one scanner in operation. A second scanner would support expansion of MRI projects involving clinical and laboratory studies. The requested amount represents the cost of the scanner and the peripheral equipment required for its operation.

Funding is necessary to equip new surgical suities that are expected to become operational during FY 1987. Although the construction costs would not come from Clinical Center funds, the additional equipment is required to make the sites functional.

Collaborative Computer Science Initiative: $4.1 million and 4 FTE's would provide for the development of a system to perform Literature Searches via Medline and transmission of data to personal computers in support of patient care. Computer center establishment of local area networks and the installation of an uninterruptible power supply to prevent loss of vital research and patient care data would be provided for within the requested level.

Scientific/Biomedical Equipment: $1.6 million would provide for the purchase of equipment to aid in the examination of contractile polymers; pharmacokenetics drug mixing; catheter development and the coestrusion of specialized tubing. Funds are also included to aquire a permanent magnetic system to improve biomedical engineering expertise in the field of NMR imaging. Additional funds are requested to expand the NIH Scientific Equipment Rental program, a pool of general utility laboratory apparatus and equipment utilized by intramural scientists in basic research applications. This program has proven to be extremely cost effective and popular among NIH clinical and laboratory investigators.

Research Animal Programs: $.7 million is requested to recondition the animal cage washing equipment in building 14A and to erect an environmentally controlled rabbit facility to house 500 rabbits for antiserum production. Included within this request are funds to renovate the embryo - cryopreservation area.

NIH Library Improvements: $.9 million is requested for alterations to obtain optimum utilization of space, improve work flow and service through increased automation usage, and cover the increased cost of binding large numbers of journals.

Engineering, Safety and Health Management: $.3 million is requested for a Computer Assisted Design and Drafting System to enhance the quality of the architectural and engineering services provided to the Institutes on the Bethesda campus at the NIH Animal Center. Funds are provided to enhance the quality of the NIH protection and security program through the recruitment of higher level professionals with recognized expertise in physical security disciplines. Funds are also requested to perform essential decontamination and recertification procedures for biological safety cabinets, chemical fume hoods and primary barrier safety equipment all associated with the modernization program of the Clinical center. Additional funds are needed to fulfill an interagency agreement with the National Bureau of Standards which requires that NIH institute a research study to obtain data concerning the use of sprinkler systems in biomedical research labs and patient care areas.

Data Management and Administrative Support: $2.1 million and 9 FTE's are provided to assist in the implementation of a new DHHS Personnel/Payroll System at the NIH computer center. Funds are also included to assist in training, maintenance and post - installation problem solving of the Financial Automated Integraded Management System. Support of Cullinet System applications training associated with the administrative data base is also contained in this request.

National Institutes of Health

HHS-Related Grace Commission Recommendations

(In millions of dollars)

I. Items Included for the First Time

Cost Control Item(s)	Grace 3-Year Savings	HHS FY 1987 Budget	HHS Rationale
	$	$	

The NIH has no recommendations included for the First Time in FY 1987.

II. Cumulative Savings - Past and Current Items - continued

Cost Control Item(s) [1/]	Grace 3-Year Savings	Actual Savings Through FY 1986	Projected Savings FY 1987
PHS 1-1 Establish a ceiling on allowable administrative costs within the Grants and Contracts process.	$ 66	$ N/A	$ N/A
PHS 1-2 Eliminate funding for equipment from research grant applications.	256	N/A	N/A
PHS 1-3 Reduce allowable grantee overhead in grant applications by 10 percent.	232	N/A	N/A
PHS 8-1 Close the Rocky Mountain Laboratory (RML) of NIH.	14	N/A	N/A
PHS 8-2 Alternative to 8-1. Fund the activity of the RML as an extramural research project.	--	N/A	N/A

Research Career Training Grants			
PHS 6-1 Reduce the number of basic research trainees supported by institutional grants by 800 and increase trainees in speciality areas supported through individual grants by 400.	17	N/A	N/A

1/ Based upon discussions held with the Department, no further actions or savings are planned for these proposals in FY 1986 or 1987.

National Institutes of Health

Management Improvement Initiatives
(dollars in thousands)

	Fiscal 1986			Fiscal 1987			Cumulative		
	BA	Outlays	FTE	BA	Outlays	FTE	BA	Outlays	FTE
Operations streamlining of the Social Security Admin........	N/A								
AFDC quality control process...	N/A								
Annual wage reporting..........	N/A								
Administrationof Social Security benefits for retired railroad workers......................	N/A								
Medicaid third-party liability.	N/A								
Regional office consolidation..	N/A								
Productivity reviews (A-76)....	--	--	--	--	--	--	--	--	--
Refinement of automated systems in support of admin. functions	N/A								
Consolidate and reorganize personnel operations......1/	--	--	--	--	--	--	--	--	--
Consolidate administrative payment centers..............	N/A								
Debt collection program........	N/A								
Close printing plants......2/	--	--	--	--	--	--	--	--	--
Space reduction...............	--	--	--	--	--	--	--	--	--
Grades 11-15 reduction.....3/	--	--	--	--	--	--	--	--	--

NB amounts are to represent savings resulting from management initiativesin each area.

1/ Initial savings took place in FY 1985; further savings not yet identified.

2/ Based on discussion with the Department, NIH plant is being converted to high-speed copy center. No savings will occur in FY 1986 or 1987.

3/ Project to be discussed with the Department. No savings have been estimated.

A-11-24D

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
RENTAL PAYMENTS to GSA

	1985 estimate	1986 estimate	1987 estimate
A. Space Occupied: (square feet in millions):			
Space Occupied as of March 15, 1984			
Office Space	.461	.461	.461
Other	.344	.344	.344
Total Base Space	.805	.805	.805
Workspace Management Reform Program			
Expansion (Planned in CY; Estimate in BY)			
Office Space	---	---	---
Other	---	---	---
Total Expansion	---	---	---
Reduction (Planned in CY; Estimate in BY)			
Office Space	---	---	-.034
Other	---	---	---
Total Reduction	---	---	-.034 3/
Total Space Required			
Office Space	.461	.461	.427
Other	.344	.344	.344
Total Space Required	.805	.805	.771

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
RENTAL PAYMENTS to GSA

A-11-24D

	1985 estimate	1986 estimate	1987 estimate
B. Rental Payments:			
Standard Level User Charge (SLUC):			
(in thousands of dollars)			
Office Space Cost.................	$ 5,991	$ 5,833	$ 5,697
Other Space Cost	1,426	1,387	1,336
Total Base Costs	7,417	7,220	7,033
Office Expansion	---	---	---
Total Expansion	---	---	---
Office Reduction	---	---	---
Total Reduction	---	---	---
Total SLUC (object class 23.1)	7,417	7,220	7,033
Rental Payments for Extra Services			
Total (object class 25.0)	1,818	1,491	2,076
Cost per square foot of office space for standard level of services.....	$ 13.00	$ 12.65	$ 13.34

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
RENTAL PAYMENTS to GSA

A-11-24D

	1985 estimate	1986 estimate	1987 estimate
C. Personnel Housed in GSA Controlled Space			
Total FTE Employment:	2,917	2,927	2,927
Cyclical Requirements	10	10	10
Non Federal Employees	68 2/	68 2/	68 2/
Subtotal	78	78	78
Department Total	2,995	3,005	3,005
Amount of office space per person:	158	157	146

1/ This space reduction represents the Westwood Towers Building Lease termination effective June 30, 1984.

2/ This figure represents employees in the Blind Industries Services of Maryland vending areas, the NIH Recreation and Welfare Association area, the Contract Guard Services and the Contract Cleaning Services.

3/ This figure reflects a reduction in space in accordance with the instructions contained in the memorandum from the Chief, BIRS, PHS dated May 20, 1985.

Prepared by Brian J. Rooney
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Revised June 4, 1985

FULL INDIRECT COSTS IN 1987

Mr. Natcher. Please provide for the record a table showing for competing research project grants for 1987 the number, amount, payline, award rate, and average cost, assuming that no limit is placed on indirect costs.

Dr. Wyngaarden. The following table shows the effect on competing research project grants in 1987 assuming full indirect costs.

DHHS-NATIONAL INSTITUTES OF HEALTH

COMPETING RESEARCH PROJECT GRANTS
(Dollars in thousands)

	FY 1987 President's Budget					FY 1987 Assuming Full Indirect Cost				
	No.	Amount	Pay-Line	Award Rate	Avg. Cost	No.	Amount	Pay-Line	Award Rate	Avg. Cost
NCI..................	874	$149,070	160	26.8%	$170.6	797	$139,035	160	24.4%	$174.4
NHLBI................	802	145,635	180	29.9	181.6	708	133,520	170	26.4	188.6
NIDR.................	110	12,683	190	31.3	115.3	100	11,671	190	28.4	116.7
NIDDK................	566	82,627	160	29.9	146.0	516	76,445	160	27.2	148.1
NINCDS...............	538	80,126	140	22.5	148.9	479	74,332	140	20.1	155.2
NIAID................	421	58,126	150	26.7	138.1	366	53,032	150	23.2	144.9
NIGMS................	689	100,867	150	30.7	146.4	596	92,295	150	26.5	154.9
NICHD................	456	62,826	160	24.6	137.8	411	58,751	160	22.2	142.9
NEI..................	250	33,869	170	35.8	135.5	222	31,061	170	31.8	139.9
NIEHS................	105	15,301	190	25.2	145.7	96	13,596	180	23.0	141.6
NIA..................	145	23,502	190	25.0	162.1	124	21,485	180	21.4	173.3
NIAMSD...............	148	19,909	160	22.6	134.5	133	18,238	160	20.3	137.1
TOTAL, NIH.......	5104	784,541	160	27.4	153.7	4548	723,461	160	24.4	159.1

ARTHRITIS INSTITUTE

Mr. Conte. Last year, as part of the NIH reauthorization bill, the new National Institute of Arthritis, Musculoskeletal and Skin Diseases was authorized, primarily over a concern as to whether enough resources were being applied to arthritis to bring about significant advances in that area. Where are you in the process of setting up a new Institute?

Dr. Wyngaarden. The NIH will soon establish a new Institute, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMSD). A separate appropriation of $106.7 million is requested for NIAMSD in the FY 1987 request. The new Institute will primarily be composed of those extramural programs currently sponsored by the Division of Arthritis and Musculoskeletal and Skin Diseases and related laboratories from the intramural program. The remaining programs will be renamed the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDKD).

The NIH will implement the change in three phases:

Phase I will occur in FY 1986 when designation of the new Institutes and selection of permanent Directors will take place. During this phase, NIH will take steps to establish independent advisory councils for the peer review process of each Institute while the current Council will continue to serve the peer-review needs of both Institutes.

Phase II will occur in FY 1987, and beginning with this year, both Institutes will function with separate appropriations and advisory councils. During this transition year, most Arthritis Institute staff offices will become functional. During FY 1987, some sharing of resources will continue between the two Institutes, particularly in the areas of grants and contracts management, personnel management, and logistical support contracts. By FY 1987, both Institutes will occupy fully independent space.

In FY 1988 Phase III will take place and both Institutes will become completely autonomous in terms of fiscal, personnel, and other resources, if the needed additional resoures are appropriated.

Mr. Conte. What level of funding is requested for this new Institute for FY 1987, and how does this compare with the historical level of funding for this area, when it was a division of NIADDK?

Dr. Wyngaarden. In FY 1987 we are requesting $106,733,000 for the new Institute. This compares to $108,800,000 in FY 1985 and $109,788,000 under the FY 1986 revised level.

Mr. Conte. Do you have any suggestions as to where this new Institute should end up in terms of size?

Dr. Wyngaarden. The ultimate size of the new Institute will depend upon the interaction of several factors: 1) the peer review system to determine scientific merit of investigator-initiated research project grant proposals; 2) the advice of national advisory councils and their role in program planning; 3) the results of assessments of the public health importance of various diseases; 4) the state of knowledge in relevant areas of science; 5) the views and concerns of the public as expressed through the Congress and by representatives of various constituency groups; and 6) the availability of funding and staffing resources.

REAUTHORIZATION

Mr. Conte. For the record, will you list the major changes and requirements of the reauthorization upon NIH, and indicate how those are reflected in the proposed budget.

Dr. Wyngaarden. The major changes and requirements of the reauthorization act entitled "The Health Research Extension Act of 1985" (P.L. 99-158) are expressed either through specific authorizations of dollars or by new requirements without authorization levels provided. Major provisions of the reauthorization reflected in the FY 1987 President's Budget request for the NIH include:

- o Specific Dollar Authorizations
  - For the research and cancer control programs of the National Cancer Institute, the FY 1987 budget requests $1,129,479,000 compared to the $1,344,000,000 authorized by P.L. 99-158.
  - For the research and control programs of the National Heart, Lung, and Blood Institute, the FY 1987 budget requests $785,697,000 compared to the $961,000,000 authorized by P.L. 99-158.
  - P.L. 99-158 authorized a total of $260,000,000 in FY 1987 for National Research Service Awards funded by the NIH; the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA); and the Health Resources and Services Administration (HRSA). The total FY 1987 request for NIH research training is $198,204,000.
  - The reauthorization act specifically authorized $2,500,000 to remain available through FY 1989 for the creation of an Alzheimer disease registry. This amount was appropriated in FY 1986 and the National Institute on Aging has issued a request for applications.
- o No Specific Dollar Authorization
  - As required by the reauthorizing act, the NIH budget request for FY 1987 reflects the establishment of two new NIH Institutes: the National Institute for Arthritis and Musculoskeletal and Skin Diseases (NIAMSD) and the National Instiute of Diabetes and Digestive and Kidney Diseases (NIDDK).
  - Though no funds are requested in FY 1987 for nursing research programs, NIH and HRSA are currently proceeding with the necessary actions to establish a National Center for Nursing Research at the NIH as required by P.L. 99-158.

- Finally, P.L. 99-158 included various other provisions relating to the establishment of Associate Directors for Prevention within NIH; the requirement of additional new reports and studies; and the creation of several new committees. NIH intends to implement each of these requirements.

RESEARCH ADVANCES

Mr. Conte. In your statement, Dr. Wyngaarden, you say that just 12 recent advances have saved about $2.5 billion in annual health care costs. What advances are you talking about there?

Dr. Wyngaarden. In an informal survey conducted at the NIH, the Institutes identified numerous advances in biomedical research that have resulted in significant savings in annual health care costs. The 12 particular advances to which I referred in my opening statement are the following:

- o Treatment of patent ductus syndrome--a heart defect of infants--with the drug indomethacin rather than through surgery.

- o Management of coronary artery disease through medical care and drugs rather than by surgery.

- o Prevention of stroke and stroke death by prescribed aspirin and standard hypertension control rather than through complicated neurosurgery.

- o Prevention of respiratory distress syndrome (RDS) in infants through steroid treatment before birth.

- o Diagnostic imaging techniques applied to brain tumors and other cancers.

- o Wide local excision and radiation, rather than amputation, for treatment of soft tissue cancers.

- o Laser treatment for three eye disorders--angle-closure glaucoma, diabetic retinopathy, and aging-related maculopathy. [Note: This entry comprises 3 of the 12 research advances.]

- o Percutaneous transluminal coronary angioplasty rather than coronary artery bypass graft procedures for single vessel atherosclerosis.

- o Accurate assessment of fetal maturity to prevent prematurity associated with cesarean delivery.

- o Development of specific criteria on which to base decisions on whether surgery is indicated in recurrent throat infections, thus decreasing unnecessary tonsillectomies.

Mr. Conte. More generally, what do you say about the statement that some folks make that all research does is to come up with high tech treatments that end up driving up the cost of medical care?

Dr. Wyngaarden. In spite of the high cost of contemporary medicine, I believe that if we persist in our research, one by one these expensive technologies, which are undoubtedly effective, even lifesaving, will be rendered as obsolete as the iron lung and replaced by yet more effective, simpler, inexpensive measures. It is also important to note that a great deal of our research is devoted to the prevention of disease. For example, if we can ultimately prevent end-stage renal disease, the expensive treatments involving kidney dialysis machines will no longer be necessary--just as the polio vaccine eliminated the iron lung.

ANIMAL RESEARCH

Mr. Conte. Last year, Doctor, there was a lot of outcry both here in Congress and out in Bethesda over the conduct of some animal research at the University of Pennsylvania. From your standpoint, is that particular issue now fully resolved?

Dr. Wyngaarden. Based on an intensive evaluation of the University of Pennsylvania's laboratory animal care and use program, the NIH has removed the temporary restraints on new commitments of funds for laboratory animal research to the University of Pennsylvania. This action does not rescind any restrictions previously placed on research involving nonhuman primates at the University's Experimental Head Injury Laboratory.

The NIH has provisionally accepted the University's animal welfare assurance document, which describes an acceptable program for laboratory animal care and use at the University. Although not yet fully implemented, the program meets the provisions of the Public Health Service animal welfare policy and the NIH Guide for the Care and Use of Laboratory Animals.

Mr. Conte. Recently, I saw a newspaper article saying that you had suspended NIH funding at another University. First of all, Doctor, who at the NIH has responsibility for policing research facilities? Does each Institute follow its own grantees, or is it a centralized function?

Dr. Wyngaarden. Oversight responsibility is shared by the NIH Office for Protection from Research Risks (OPRR) and by the Institutes, which monitor the progress of awards, ensure that the appropriate institutional animal care and use committee review has occurred, and that concerns identified during the review process are resolved.

The OPRR is responsible for the administration of the PHS Policy on Humane Care and Use of Laboratory Animals, and requires that all institutions, in order to be eligible to receive funds for an award involving animals, submit an acceptable Animal Welfare Assurance that describes an adequate program for the care and use of animals and commits the institution to comply with the PHS Policy and the Animal Welfare Act, as well as all other applicable guidelines, laws, and regulations. OPRR also conducts site visits to institutions, both announced and unannounced, to assess the adequacy of an institution's compliance with the PHS Policy. When necessary, the OPRR conducts investigations into alleged violations of the PHS

Policy. The results of such investigations are reported to the Director, NIH, or other Agency heads, who have authority to suspend funds when necessary.

Mr. Conte. Do you think the NIH is doing enough to ensure that both intra- and extramural animal research is conducted in the most proper and humane environment?

Dr. Wyngaarden. Intra- and extramural NIH approaches concerning animal care and use are consistent and handled in a similar fashion. Intramurally, NIH's efforts to conduct animal research humanely and in a proper environment have been intensified during recent years. Salient features of current intramural policies, practices, and initiatives are as follows:

- o The Director, NIH, has instructed that all intramural animal care and use activities be accreditable by the American Association for Accreditation of Laboratory Animal Care (AAALAC) by early FY 1988. Eighty percent of the animal space/program at NIH is currently AAALAC accredited, and an accelerated program is proceeding to bring the remainder into compliance. In the planning process, consideration is being given to replacing decentralized animal holding with several centralized animal facilities so as to facilitate management and assure adherence to animal care and use policies. It is estimated that the necessary renovations/construction will cost about $13 million.

- o Animal Research Committees in each of the Institutes have played increasingly important roles, since 1983, in assessing and assuring compliance with NIH policy as described in the DHHS Guide for the Care and Use of Laboratory Animals and the NIH Principles for Use of Animals. For example, these bodies are charged with reviewing all research involving animals for adherence to humane and ethical practices, site-visiting, and evaluating areas where animals are housed and used, as well as advising and making recommendations to BID Scientific Directors and to individual investigators on all matters related to animal care.

- o Each Institute has been provided with the services of veterinarians to consult with, advise, and work with scientists on animal care and use practices. These veterinarians are also intimately involved in the planning process for AAALAC accreditation.

- o In addition to training for technicians that has been available for years through the American Association of Laboratory Animal Science, the NIH designed and implemented a course in 1984 mainly for intramural investigators involved in animal care and use. This course is offered quarterly and provides information on techniques and available resources as well as considering legal requirements, ethical and humane issues, and NIH policy.

- o Most recently, an educational compaign entitled "NIH Animal Awareness" was established to increase sensitivity concerning research animal issues among all employees at the NIH.

Thus the NIH intramural program has instituted methods for monitoring the adequacy of environments provided for its research animals and is currently aiming toward achieving AAALAC accreditation of all such space in FY 1988. Procedures are currently in place to review all animal research for adherence to humane principles and ethical practices. In addition, a training program is in place to provide investigators with information concerning legal requirements, ethical issues, and technical information involving the use of laboratory animals.

To ensure that extramural animal research is conducted in the most humane manner possible, recent NIH activities have included the following:

- o Revision of the PHS Animal Welfare Policy, which requires all awardee institutions to submit to NIH an Animal Welfare Assurance, describing an acceptable program for laboratory animals and committing the institution to compliance with the PHS Policy, the NIH Guide for the Care and Use of Laboratory Animals, the Animal Welfare Act, and all other applicable laws and regulations. The revised policy is substantially stronger than the 1979 policy, and requires an expanded Institutional Animal Care and Use Committee with responsibility for protocol review.

- o A series of site visits to assess the adequacy of the assurance system. Many of the specific policy revisions were a result of recommendations arising from these site visits. The random site visits will continue through 1988.

- o A series of regional educational workshops to assist awardee institutions in understanding their responsibilities and implementing a successful program of laboratory animal care and use.

- o Conducting investigations, when necessary, into alleged violations of the PHS Animal Welfare Policy.

Mr. Conte. In the last year, I believe, the NIH issued revised standards for the care and treatment of laboratory animals. Do you think these new guidelines are tougher, and that perhaps we'll see more grantee funds suspended in the coming months?

Dr. Wyngaarden. As stated above, the new PHS policy is considerably stronger than the 1979 policy. Problems that we have found in the past, and consider to be of a serious nature, include inactive and ineffective Animal Care Committees, loosely organized programs without effective administrative structures and well-defined responsibilities, and lack of procedures and mechanisms for solving day to day problems that occur in any program.

The new policy specifically addresses these problems and requires institutions to provide details in their Assurance information concerning their program that will alert us if these kinds of problems exist. For example, the new policy clearly defines the role and responsibilities of Animal Care Committees and is intended to enhance the involvement of such committees in the institution's program for animal care and use. Further, the policy requires institutions to specify, in their Assurance, how the Animal Care Committee will fulfill each of the functions outlined in the policy. We do not anticipate finding these kinds of problems to the extent that they existed prior to the new policy. Although some institutions will need a considerable amount of guidance, for example, in developing a program with clear lines of authority and responsibility, we believe that an acceptable program can be established at most institutions.

Mr. Conte. OTA recently issued a report on alternatives to animal use in research, and one of the issues they spoke to was the lack or absence of funding for projects to develop alternative models to animal research. I've got some doctors up in my District working on computer simulations for human surgery and perhaps that could be expanded. Do you think the NIH should be looking to fund these kinds of projects?

Dr. Wyngaarden. Yes; NIH is looking into the need to fund further investigation into research methods that do not use animals. An NIH-wide plan is being developed as called for in P.L. 99-158, Section 4. Serving as a foundation for the plan's development is the in-depth evaluation of the use of simple model systems in biomedical research, which NIH conducted through contract with the National Academy of Sciences (NAS). The evaluation report, Models for Biomedical Research: A New Perspective, deals with the opportunities and limitations to the use of cells and tissues, lower organisms, and mathematical and computer simulations as model systems in biomedical research. Projects using these kinds of model systems are supported by NIH. The NAS report on models provides information about this funding. We intend to make careful examination of the Academy's suggestion that NIH consider the adequacy of current funding for these types of models. The Division of Research Resources' Biomedical Research Technology Resources Program currently supports several computer resource centers, one of which is specifically devoted to biomedical simulations.

AFFIRMATIVE ACTION

Mr. Conte. Doctor, two weeks ago we had the Secretary of Labor up here and he's a strong supporter of Affirmative Action. That's good; that's what we like on this Subcommittee. My friends Lou Stokes and Steny Hoyer do a good job making sure we live up to our obligations, especially in the Federal Government. I assume you've seen what the GAO did for them on NIH Affirmative Action efforts. I just got a copy myself, and they've leveled two serious charges at you: One, that it takes far too long for NIH to process employee discrimination complaints, and two, that NIH has failed even to comply with half of the Equal Employment Opportunity Commission's requirements for Federal Affirmative Actions programs. Doctor, we look to NIH to be the model, the leader around here of what is good about the Federal Government. Tell me generally your response to that report and what is needed to correct these problems.

Dr. Wyngaarden. The GAO report noted that during FYs 1982 and 1984, the NIH, compared to other PHS agencies, took the longest number of days to process complaints of discrimination. The GAO also noted that during FYs 1984 and 1985, the NIH took certain actions to improve processing time, and that these actions appear to be reasonable. Additionally, it was noted that the NIH issued 41 proposed dispositions between August 1984 and December 1985, thus eliminating a long-standing backlog of discrimination complaints. The median number of days taken by NIH to process discrimination complaints declined significantly from 395.5 days in FY 1984 to 137 days in FY 1986, facts made known to the GAO study team but not included in the report. It has been determined that no further corrective action is needed in this area.

In the area of affirmative action, the GAO report noted that NIH was not fully complying with affirmative action requirements. The U.S. Office of Personnel Management's position on the collection of applicant data has seriously impacted on NIH's ability to comply with two Federal requirements for affirmative action. The lack of OMB authorization of a form on which to collect data on the race, ethnic origin, and gender of applicants has caused Federal agencies, including the NIH, to be unable to collect the EEOC required data. This matter has also impacted on the ability of NIH to conduct barrier analyses that are considered "adequate" by the EEOC because of the lack of applicant data. NIH will proceed with completing the remaining barrier analyses absent applicant data.

As for the remaining two areas, the NIH has undertaken steps to fully comply with EEOC affirmative action requirements. A committee has been established to develop a methodology for establishing meaningful goals and for their implementation in NIH Bureaus, Institutes, and Divisions. Once established, these hiring goals will be circulated to NIH organizational components. The Director, NIH, will instruct the five components that do not have minority and female recruiting plans to develop and submit them to the NIH Division of Equal Opportunity.

Mr. Conte. I know there has been confusion with both the Equal Employment Commission and the Office of Personnel Management over what is "required procedure and what is simply "encouraged" procedure. But I can tell you that we on this Subcommittee want you to be out ahead on this sort of thing. What are your specific aims in terms of developing hiring goals, effective recruitment strategies, and data collection that would help eliminate barriers to minorities and women?

Dr. Wyngaarden. The intention of the NIH in developing hiring goals and effective recruitment strategies will be to improve the representation of racial and ethnic minorities, women, and disabled persons in the NIH work force through implementation of specific affirmative employment actions. We believe that considerable progress has been made already -- 52 percent of NIH employees are women, and 30 percent are minorities -- far more than most Federal agencies. We do agree, however, that we are deficient at higher grade levels due to educational and experience requirements.

As mentioned above, a committee has been established to develop a methodology for developing meaningful goals and for their implementation in NIH Bureaus, Institutes, and Divisions.

In February 1984, the Director, Division of Equal Opportunity, and the Director, Division of Personnel Management, jointly requested written clarification on the collection of applicant data from the DHHS Assistant Secretary for Personnel Administration, who in turn sought guidance from the U.S. Office of Personnel Management (OPM). The DHHS was unable to resolve this matter with OPM. Until this issue is resolved, NIH will be unable to meet this affirmative action requirement. The inability to collect these data will impact on the "adequacy" of barrier analyses being conducted by the NIH.

INSTRUMENTATION

Mr. Conte. Recently, I believe, NIH and the NIH Advisory Council took another look at where we stand on the instrumentation issue. How have the increases we have provided to instrumentation grants done in alleviating the inadequate instrumentation of our nation's research facilities, and where should we be going from here?

Dr. Wyngaarden. The recent appropriation increases provided by the Congress to alleviate the problem of inadequate instrumentation at our Nation's research facilities have done much to improve our research capabilities. However, our task has been not only to reequip and refurbish outdated, obsolete equipment in biomedical laboratories, but also to ensure that our biomedical researchers have access to state-of-the-art sophisticated instrumentation. Instrumentation is not only an acute problem today but will continue to be a problem in the future because technological progress quickly renders instrumentation obsolete. In just the last 3 to 4 years, several new experimental methods have come into existence that have revolutionized many areas of medical science.

The BRS Shared Instrumentation Grant Program, supported by the Division of Research Resources, has been helpful in alleviating the problems of acquiring complex instrumentation for both basic and clinical scientists. However, the rate at which instrumentation becomes non-state-of-the-art has shortened their useful life. Sustained investment is required to keep institutions equipped with modern instrumentation, to keep our scientists competitive with those in foreign countries, and to keep our biomedical scientists at the cutting edge of research. There is a need to revitalize continually the instrumentation base on which future scientific and technological advances depend.

In a recent survey of academic research equipment and equipment needs in university departments of biological and medical sciences, nearly 60 percent of department heads reported that there are important subject areas that cannot be addressed because of lack of necessary equipment. Department heads assessed the adequacy of the instrumentation in place in 1983 as: excellent, 16 percent; adequate, 57 percent; insufficient, 27 percent.

At the NIH, approximately 4.2 percent of the total extramural dollars available are spent on instrumentation, which represents a positive indication of our investment in research instrumentation. Despite increased funding for instrumentation in recent years, the instrumentation survey indicates that NIH should pay greater attention to instrumentation in the $10,000 to $60,000 range. This is primarily the category involving replacement of barely functioning, worn out, or inadequate equipment which should be replenished through the research project grant mechanism. NIH will continue to maintain the BRS Shared Instrumentation Grant Program at a level of $31.4 million in 1987, which is approximately the same level as in 1985 and 1986.

FACILITIES

Mr. Conte. Last year, the budget proposed continuing construction grants for several of the Institutes, but this year, the budget proposes zeroing out those activities, I believe. Why the change of position here?

Dr. Wyngaarden. The FY 1987 budget request proposes elimination of the extramural facilities construction program. While termination of this program in FY 1987 may cause the postponement of some research facilities construction, constrained resources have required many difficult funding decisions. The extramural facilities construction program represents a relatively lower priority when compared to other important research activities and when viewed in the context of limited fiscal resources.

BRSG's

Mr. Conte. The budget also proposes eliminating Biomedical Research Support Grants, which provide formula grants to institutions receiving NIH support, to provide a flexible pool of funds to initiate or support research efforts. Why have you supported this program in the past and why are you now proposing to eliminate it?

Dr. Wyngaarden. The BRSG program is one of three subactivities in the Biomedical Research Support program funded by the Division of Research Resources. The objective of this program has been to strengthen and enhance the research environments of institutions heavily engaged in health-related research. The program provides each research institution, which receives a minimum of $200,000 in PHS research grants and which meets several other requirements, with additional funds proportional to the size of the research grant.

The most common use of these funds has been for small pilot projects and for interim funding between grant-supported projects. The program permits the grantee institution to make its own judgments and decisions at the local level over emphasis, direction, content, and quality of its biomedical research efforts. Thus, phaseout of this program will eliminate some of this type of support.

While this has been a valuable program, in view of the growing concern for the budget deficit, the BRSG program, which provides generalized institutional support, must rank as a lower priority when compared to other NIH programs which permit the focusing of research funds to specific priority areas.

PRIVATE RESEARCH SUPPORT

Mr. Conte. Recently, the role of private support for biomedical research has been highlighted by the announcement by the Hughes

Institute of $1 billion of grants to institutions across the country. How was private support for biomedical research increased over the past few years, and how does this impact upon the need for Federal support of biomedical research?

Dr. Wyngaarden. The announcement by the Howard Hughes Medical Institute (HHMI) in Feburary of this year indicating its plans to spend $1 billion for medical research support over the next 5 years (1986-1990) has focused attention on the role of private support of biomedical and health-related research and the relationship of such support to Federal investments in this area.

By way of background, it is useful to keep in mind that the relative contribution of private, non-profit support for biomedical and health-related research has decreased over the last 10 years. In 1975, private, non-profit organizations provided $264 million compared to the Federal Government's $2.8 billion. In 1985, these organizations invested $377 million compared to the Federal Government's $6.9 billion.

Against this background, the recently announced HHMI investments are particularly welcomed. HHMI, unlike the NIH, does not award grants to individual scientists, but rather awards funds to a research organization for use by its own scientists working on the organization's intramural research programs. The HHMI plans to devote approximately 30 percent of the 5-year total (or about $300 million) to construction of new facilities, renovation of existing ones, and purchase and upkeep of medical research instruments--in order to improve and strengthen the biomedical research capabilities at the Nation's premier academic medical centers. The remaining $700 million will focus on training of new researchers and support of established ones in the critical fields of genetics, immunology, metabolic regulation, and neurosciences. Funds will be awarded to the 22 HHMI laboratories already active or to be established in academic medical centers and their teaching hospitals in 14 states. The HHMI funding plans for training and research support will add an additional $700 million to a projected $2.1 billion of similar support from other private, non-profit agencies during the same 5-year period. The addition of such new money to the Nation's support of biomedical research does not, however, reduce the need for Federal Government support.

Another aspect of non-Governmental support of biomedical research of considerable interest to NIH is the emerging investments in biotechnology research at universities by the biotechnology industry. As pointed out in a January 17, 1986 Science article by David Blumenthal et. al. ("Industrial Support of University Research in Biotechnology"), nearly one-half of the firms fund such research in selected schools. This amounted to an estimated $120.7 million in 1984. At the same time, NIH provided an estimated $1.64 billion for biotechnology-related extramural research support (most of which went to the Nation's academic centers). This was made up of approximately $0.52 billion in basic research directly related to biotechnology (such as genetic manipulation, cloning of DNA, creation of hybridomas) and $1.12 billion for undifferentiated research in basic bioscience areas underlying further progress in biotechnology (such as molecular biology, genetics, immunology, and related topics).

Viewed in this context, the biotechnology industry investment remains comparatively small. It also has a specialized purpose: It is driven primarily by commercial objectives. While it may focus on basic research, it is directed toward patentable processes or products, commercial success and expansion, and new services and products for the national and international marketplace. In terms of national policy, however, this industry-university relationship facilitates the accelerated translation of goods and services into the economic mainstream where they can promote economic growth and the national welfare.

The Federal investment, of course, is designed to ensure the stable and continuing growth in the knowledge base necessary to enhance the intellectual infrastructure on which all more focused research and development, whether in the public or private sector, must build. This is a time-honored public role that has not been assumed by the private sector, nor is it expected to be.

Industry support for biotechnology research is not and should not be considered a substitute for Federal support.

QUALITY OF CARE AT NIH CLINICAL CENTER

Mr. Conte. Over the past year, it seems that we have read of a number of incidents at NIH in which patients have died or have gone into comas. Have you followed through on these incidents with investigations as to what went wrong?

Dr. Wyngaarden. All patients at the Clinical Center are involved in biomedical research protocols which vary widely depending upon the area of research interest on the part of a particular Institute. Accordingly, coma as an intermediate or end stage of an illness might be far more likely to occur (and thus be expected), for example, in programs of the National Cancer Institute, the National Institute of Neurological and Communicative Disorders and Stroke, or the National Heart, Lung, and Blood Institute, where patients' illness are often more severe or extensive than in the National Institute on Aging, National Eye Institute, or National Institute of Dental Research.

Rare cases of unanticipated coma are intensively investigated, as occurred with an infant who died from misadministration of an incorrect intravenous fluid. By way of example, as a result of that case, specific changes were made in a number of medical, nursing, and hospital supply practices, and non-Federal organizations were contacted about an ambiguity in the labeling of the lethal pharmacological agent that caused the patient's death. In another case, a fatal complication of a high risk but commonly performed diagnostic procedure led to a subsequent change in the technical approach used.

The Clinical Center has developed a broad-based program of quality assurance whose components identify potential or actual problems associated with clinical care as well as maintain a safe environment for all who use the facilities. These components include an incident reporting system; a careful physician credentialing process; an active patient advocate function; detailed informed consent procedures; monthly reports related to the quality and appropriateness of care required of all clinical services; and targeted reviews by subcommittees of the Medical Board in such areas as the use of blood products and pharmaceutical agents. Clinical Center administrative officials are promptly notified of untoward events on a case-by-case basis whenever in the judgment of the attending physicians the outcome of a treatment or procedure is regarded as a major, or irreversible, unanticipated complication or outcome.

In general, clinical services also conduct morbidity and mortality reviews on a regular basis, evaluating clinical outcomes for educational purposes as well as to alter procedures, techniques, or clinical approaches where that seems indicated.

Mr. Conte. Are there any areas in which you have turned up inadequacies in the care of patients?

Dr. Wyngaarden. The Clinical Center's Quality Assurance Program monitors the quality and appropriateness of care. Adverse or untoward occurrences involving patients are vigorously pursued in order to better understand a particular event and determine what actions are required to resolve the problem; these actions may occur at the level of health care provider, support services, technology, or administrative management.

Quarterly reports to the Hospital's Quality Assurance Committee, the Medical Board and Service Chiefs provide a continuous inventory of occurrences in broad categories: traumas; errors in medication or fluid administration; problems with treatments/diagnostic procedures; dietary-related issues; and a miscellaneous group which includes equipment malfunctions and building maintenance problems. These data are used by clinical services to detect and track patterns of adverse occurrences as well as to forestall or remedy them. The adequacy of medical care is reviewed by Institute Clinical Directors and by the Clinical Center Medical Board. The hospital itself is regularly reviewed by the Joint Commission on Accreditation of Hospitals.

It should be noted that most of the occurrences reported are minor and have not led to patient harm; the relatively few incidents that have resulted in an adverse patient outcome, or that are regarded as having had the potential for doing so, are subjected to careful follow-up, evaluation, and resolution.

Mr. Conte. When you settle a case, where does the money to pay that settlement come from?

Dr. Wyngaarden. The funds for settlements or adverse judgments are paid from the Judgment Fund, which is administered by the Department of Justice.

TRANSFER AUTHORITY

Mr. Conte. You again propose language giving authority to transfer up to 1/2 percent of appropriations among Institutes at NIH. But there is a phrase added on to that language proposal that I would like you to explain. It says "Provided, that research grants or contracts funded by any appropriation made to any National Institute of Health or the Alcohol, Drug Abuse and Mental Health Administration, shall be awarded only after consideration by the advisory body of the full cost of such a research grant or contract.' What is this language proviso all about?

Dr. Wyngaarden. The suggested language derives largely from a recent recommendation by the Office of Science and Technology Policy that research agencies such as the NIH include total costs rather than only direct costs for review and evaluation of grant applications and contract proposals. The NIH is moving to incorporate appropriate changes into the revised standard grant application form PHS 398 and accompanying instructions to applicants. NIH requests for contract proposals already ask for total as well as direct costs. Appropriate instructions will be issued to NIH grant, contract, and review offices to ensure that total cost figures as well as direct costs will be available for consideration by the grant and contract scientific advisory review groups.

EARMARKING

Mr. Conte. In an article in Science of May 30 of last year, the former residents of the Office of Science and Technology Policy chimed in about NIH research. One of the things they said caught my eye. In that article, the authors stated that "NIH itself has calculated that approximately 25 percent of its budget is directed by the Congress toward specific diseases, projects and programs." Would you please indicate what the source of that statement is, and outline for me the 25 percent of the NIH budget that Congress has mandated you to undertake that you would not undertake otherwise?

Dr. Wyngaarden. The figure of 25 percent cited in the article in Science is, most likely, based on an estimate made by NIH in 1983 of the degree to which the use of NIH resources is conditioned by the need to respond to specific congressional mandates and directives. In developing this estimate, the NIH examined two major types of expression of congressional interest--legislative mandates contained in specific statutes or Acts, and directives expressed in language contained in the reports of appropriations committees.

It was estimated that NIH allocated approximately 8 percent of its total budget in response to specific legislative mandates; another 16 percent of its funds was spent in response to less circumscribed congressional directives expressed in appropriations reports. Therefore, an estimated total of 24 percent of the NIH budget was allocated in response to congressional mandates and directives.

Some of the major areas in which the NIH responded to direct expressions of congressional intent included: cancer control programs; multipurpose arthritis centers; diabetes research and training centers; digestive diseases information and education centers; the national toxicology program; heart, lung, and blood prevention and control programs; the Gorgas Memorial Laboratory; smoking and health; nutrition; regional instrumentation facilities; clinical trials; mental retardation research centers; sudden infant death syndrome; sexually transmitted diseases; behavioral medicine; and hypertension.

I should note that, in interpreting these data, one cannot assume that the areas of activity represented by these congressional mandates and directives would not be funded, at some level, in the absence of specific expressions of congressional interest and concern. While it is difficult to determine the degree to which these mandates and directives translate into actual budget allocations, the weight accorded these explicit statements of congressional intent plays an ever-increasing role in the competition that occurs for the funds available for biomedical research and training.

APPROPRIATIONS HISTORY

Mr. Conte. Dr. Wyngaarden, would you also indicate how much money the Congress had added to the NIH budget over and above the Administration's budget request for each year you have been Director, and indicate what amount of that funding you consider to have been unnecessary?

Dr. Wyngaarden. I became Director of the NIH in April 1982, and first appeared before this Committee in March 1983 in defense of the FY 1984 budget. I can assure you that all the funds appropriated have been effectively used.

The following list compares the amounts requested to those provided by the Congress since I have been Director of NIH:

	Request	Appropriation	Percentage Increase
FY 1984	$4,077,092,000	$4,494,782,000	10.2%
FY 1985	4,566,452,000	5,149,459,000	12.8
FY 1986	4,852,680,000	5,498,454,000	13.3

AIDS FUNDING

Mr. Roybal. The NIH budget proposes $143.9 million for AIDS. What assurances have you received from the Office of the Assistant Secretary of Health that NIH will in fact be allocated this amount?

Dr. Wyngaarden. The current anticipated reimbursement to the NIH is now estimated at $142,990,000. We have been assured that barring a dramatic change in requirements brought about by unexpected developments in this disease, the planned amounts will be readily available.

Mr. Roybal. What AIDS activities or initiatives will be altered in any way if the funding is reduced compared to the FY 1986 budget? How did you establish these priorities?

Dr. Wyngaarden. If FY 1987 funding for AIDS research were to be reduced to the FY 1986 level, approximately $120.8 million would be available; this represents a reduction of about $22.1 million from the current FY 1987 level. Within a total of $120.8 million in FY 1987, the NIH would support its ongoing programs at a reduced level; funds would not be available to begin any new initiatives.

ALZHEIMER DISEASE

Mr. Roybal. How many projects and what level of extramural funding was devoted to research on Alzheimer disease in FY 1985, expected in FY 1986 (before and after sequestration and after rescission), and proposed for FY 1987? What level of intramural effort was and will be devoted to this area of research for these same time periods? Please provide the information by Institute.

Dr. Wyngaarden. The requested information is shown in the table on the following page.

Mr. Roybal. What progress can you report on the prevention, techniques for early diagnosis, and medical management of patients with Alzheimer disease?

Dr. Wyngaarden. At present, we do not have the necessary scientific knowledge for preventing Alzheimer disease. Research supported by the National Institute on Aging, however, has identified three potential risk factors for Alzheimer disease leading toward this important goal: aging, familial ties, and head trauma. It is only after we understand how the disease comes about that we can hope to develop measures to prevent it.

Diagnosis, especially early diagnosis, is an area of particular emphasis. A planning workshop was recently held in cooperation with the American Association of Retired People to stimulate further research in diagnosis. The proceedings of the workshop were recently published in Archives of Neurology.

Several successive generations of psychological tests have begun to focus more closely on the early and progressive signs of Alzheimer disease. And now, at the Massachusetts General Hospital in Boston, an NIA grantee is using nuclear magnetic resonance (NMR),

ALZHEIMER DISEASE RESEARCH

(Dollars in thousands)

	1985		1986 Appropriation		1986 Appropriation After Sesquestration		1986 Revised		1987 Request	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Extramural										
NHLBI	1	$88	1	$90	1	$87	1	$87	--	---
NINCDS	58	11,351	59	12,549	59	12,010	58	11,700	58	$11,700
NIAID	6	877	6	917	6	877	6	872	6	872
NIA	104	23,761	116	28,811	116	27,680	112	27,083	112	27,083
DRR	59	1,034	57	1,055	55	1,010	55	1,010	30	874
Subtotal	228	37,111	239	43,422	237	41,684	232	40,752	206	40,529
Intramural										
NHLBI	--	---	--	---	--	---	--	---	--	---
NINCDS	9	1,475	9	1,481	9	1,417	9	1,417	9	1,417
NIAID	2	334	2	330	2	315	2	315	2	315
NIA	18	5,069	19	5,237	18	5,011	18	5,011	18	5,011
DRR	--	---	--	---	--	---	--	---	--	---
Subtotal	29	6,878	30	7,048	29	6,743	29	6,743	29	6,743
Total										
NHLBI	1	88	1	90	1	87	1	87	--	---
NINCDS	67	12,826	68	14,030	68	13,427	67	13,117	67	13,117
NIAID	8	1,211	8	1,247	8	1,192	8	1,187	8	1,187
NIA	122	28,830	135	34,048	134	32,691	130	32,094	130	32,094
DRR	59	1,034	57	1,055	55	1,010	55	1,010	30	874
Total, NIH	257	43,989	269	50,470	266	48,407	261	47,495	235	47,272

the latest diagnostic tool, to examine patients with Alzheimer disease and other forms of dementia. What he and his colleagues have found is that the unique ability of NMR to distinguish the brain's white and grey matter allows it to pick up abnormalities that may indicate early multi-infarct dementia. Multi-infarct dementia is the second leading cause of dementia in older people.

Whether NMR will be a valuable diagnostic tool for Alzheimer disease is difficult to predict since this technology is still in its infancy. In the meantime, findings of white matter lesions in otherwise healthy people projects the possibility of early diagnosis for at least one form of dementia. If this is indeed an early indication of multi-infarct disease, diet and life style changes may prevent further damage. Future research using NMR will be looking at those areas of the brain known to be affected in Alzheimer disease to see if changes in brain structure can be linked to changes in function as the disease progresses.

The NIA Laboratory of Neurosciences operates a Dementia Clinic to screen patients and to establish methods for the differential diagnoses and staging of the various dementias. Research results indicate that positron emission tomography (PET) shows considerable promise for early detection of Alzheimer disease. Laboratory findings show that brain atrophy can be quantitatively demonstrated with computerized transverse axial tomography (CT) scans in Alzheimer patients. Specifically, in 19 patients with Alzheimer disease, ranging in age from 45 to 81 years, quantitative analysis of CT data demonstrated that the percentage of intracranial space occupied by gray matter was reduced, and that occupied by cerebrospinal fluid was increased, as compared to values in age-matched healthy controls. Further, with respect to the severity of dementia as measured by the Mini-Mental Examination, the percentage of gray matter declined and the percentage of white matter increased. The relationships were statistically significant after partialing out age.

At present, knowledge about the medical management of patients with Alzheimer disease is very rudimentary. However, at several of the NIH Alzheimer Disease Research Centers, attempts are being made to structure the care facility in a manner designed to reduce the confusional state of the patient. At the University of Pennsylvania Geriatric Center, work is under way to study the architectural design and living space of patients to address patient management questions. At the Center in Seattle, Washington, the departments of architecture, nursing, and psychiatry are cooperating to develop innovative nursing care in new environments to improve the management of patients with Alzheimer disease.

CHANGES REQUIRED TO ACHIEVE FY 1987 BUDGET REDUCTIONS

Mr. Roybal. Given the reduction in competing grants from 6,219 in FY 1985 to 5,104 proposed for FY 1987 (comparable), what is your expectation about how much better the priority score for competing grants will have to be in FY 1987 in order to be funded? Do you anticipate any administrative actions directing how those reductions would be taken; e.g., change in the ratio of investigator-initiated to Institute-initiated grants, greater use of existing mechanisms to fund grants out of normal sequence in order to insure an adequate research base in a priority area, or the elimination of certain research areas of lesser priority?

Dr. Wyngaarden. It is certainly the case that, in order to receive funding in FY 1987, competing grants will require better priority scores than those awarded in FY 1985 and FY 1986; however, the difference in paylines between these levels will vary considerably among the Institutes. On the average, it is estimated that priority scores will need to be about 10 to 15 points better in FY 1987.

I do not anticipate any administrative actions directing how the reductions in numbers of competing awards will be determined. The Institutes will make their own funding decisions based on scientific merit and their individual research priorities.

Mr. Roybal. What are the most important research opportunities that each Institute would have to forego to absorb the FY 1987 estimated reduction of up to 13 percent from the current services level?

Dr. Wyngaarden. The FY 1987 request represents a decrease of about 11 percent from the FY 1987 current services level based on the FY 1986 estimate.

In this comparison, the areas in which the Institutes would be required to defer research opportunities crosscut all mechanisms and programs--from cancer research to research on aging. For example, the current services level when compared to the FY 1987 request would provide for an additional: 388 investigator-initiated research project grants and $424.4 million; 689 research trainees and $19.7 million; 11 research centers and $37.6 million; and $10.0 million for intramural research programs. Also, the biomedical research support formula grant (BRSG) program and the extramural construction program, which were proposed for elimination in the FY 1987 request, would be supported at $60.0 million and $8.6 million, respectively, at the FY 1987 current services level.

CLINICAL TRIALS AFFECTED BY BUDGET PROPOSAL

Mr. Roybal. Briefly describe the clinical trials which may be scientifically appropriate at this time but which will be delayed because of insufficient funds or difficulty in shifting available funds into the most appropriate mechanism.

Dr. Wyngaarden. The Institutes have identified several clinical trials which will be ready to begin in 1987, but will not be funded under the President's budget. The trials are listed by Institute and not necessarily in priority order:

MAJOR NEW CLINICAL TRIALS READY TO BEGIN IN 1987 IF FUNDS WERE AVAILABLE

(Dollars in Thousands)

	First Year Cost	Estimated Total Cost
NCI:		
Biochemical modulation of chemotherapeutic agents in colorectal, breast, stomach, and head and neck cancers........	$ 750	$ 2,200
Phase II/III clinical trials using hyperthermia in anatomical sites..........	600	1,800
Phase I/II trials of additional biological response modifiers...................	4,000	6,000
Treatment of resectable colorectal hepatic metastases with surgery followed by LAK cells/IL-2 adjuvant immunotherapy............................	575	1,725
Phase III studies of adoptive immunotherapy of cancer with autologous LAK cells and IL-2..........................	20,000	40,000 1/
Comparison of post operative radiotherapy and adjuvant chemotherapy with chemotherapy, in children with medulloblastoma................................	100	300
Phase I/II clinical trials of biological response modifiers.......................	2,000	2,500
Treatment of carcinoma of the bladder with hematoporphrin with photoradiation therapy........................	70	210
Use of TNF in patients with metastatic cancer who have failed conventional therapy.................................	1,150	3,450
Study of radiolabeled monoclonal antibodies to detect sites of Hodgkin's disease involvement......................	182	546
Subtotal, NCI....................	29,427	58,731
NHLBI:		
Bypass angioplasty revascularization investigation............................	1,000	28,600
Dietary intervention in children............	700	9,255
Coronary artery bypass graft study..........	850	29,500
Postmenopausal estrogen and coronary heart disease risk.......................	4,000	12,700
Treatment of pulmonary embolism with tPA....	1,000	10,000
Continous positive alveolar pressure treatment of sleep apneas................	800	4,000
Penicillin prophylaxis in sickle cell disease..................................	900	1,800
Post-transfusion Non-A, Non-B hepatitis study...................................	1,000	3,215
Deep vein thrombosis diagnosis and treatment................................	600	10,800
Subtotal, NHLBI..................	10,850	109,870

1/ Tentative estimate; final cost to be determined when required duration of trial is known.

NIDR:	First Year Cost	Estimated Total Cost
Diabetes control and complication trial (DCCT) oral complications	$ 150	$ 300
Clinical evaluations of the relative efficacy and safety of intravenous premedication in dental outpatients	225	425
Subtotal, NIDR	375	725
NIADDK:		
Treatment of short stature with human growth hormone	420	1,400
Nonsurgical (balloons) reduction of stomach capacity in the treatment of morbid obesity	212	464
Postoperative decompression feeding trial	4,785	25,500
Kidney transplantation in children with end-stage renal disease	250	1,000
Expanded nephrologic component of the Diabetes Control and Complications Trial	480	6,650
Controlled clinical trial of hematin therapy for acute prophyric attacks	450	2,500
Subtotal, NIDDKD	6,597	37,514
NINCDS:		
Stroke prevention medical surgical carotid stenosis study in asymptomatic patients	3,019	27,394
Stroke prevention by carotid endarterectomy in symptomatic patients	4,176	29,177
Study of cyclosporin A for the management of autoimmune disorders	500	1,575
Monoclonal antibody treatment of multiple sclerosis	500	1,575
Study of monoamine oxidase inhibitors for the treatment of Parkinson's disease	2,000	7,000
Study of orphan products for the treatment of rare movement disorders such as Tourette's syndrome	1,200	3,600
Copolymer 1 in the treatment of multiple sclerosis	2,250	6,750
Efficacy of new antiepileptic drugs in patients with complex partial seizures (two trials)	500	1,500
Subtotal, NINCDS	14,145	78,571
NIAID:		
Monoclonal antibodies in bone marrow transplantation	1,200	4,800
Efficacy trial for rDNA hepatitis B vaccines	150	600
DHPG prophylaxis of cytomegalovirus in bone marrow transplant patients	450	900
Expanded phase I and II trials of antimalarial vaccines	60	135

	First Year Cost	Estimated Total Cost
NIAID: (cont.)		
Efficacy trial for live, attenuated hepatitis A virus vaccine................	$ 150	$ 450
Study of different regimens of therapy for systemic candidiasis.................	300	1,691
Subtotal, NIAID..................	2,310	8,576
NICHD:		
Effects of growth hormone releasing factors..................................	500	2,000
Nutrition, other factors, and the outcome of pregnancy............................	150	600
Factors influencing breastfeeding..........	150	600
Mental Retardation Research Centers network of clinical trials......................	1,200	6,000
Safety and efficacy of pertussis vaccine...	2,200	8,400
Safety and efficacy of Hemophilus influenzae vaccine......................	500	1,500
Clinical studies with a long-acting spermicidal formulation..................	150	350
Tests of the use of medications to treat various maternal diseases and the safety and efficacy of various therapeutic agents to stop premature labor...........	500	2,500
Examination of current treatments in long-term management of bronchiopulmonary dysplasia, and the use of anticonvulsants in the treatment of neonatal seizures....	500	2,500
Subtotal, NICHD..................	5,850	24,450
NEI:		
Central retinal vein occlusion study.......	1,000	5,000
Treatment of optic neuropathy with steroids................................	1,500	8,000
Surgical reattachment of the retina in advanced severe retinopathy of prematurity............................	3,000	12,000
Evaluations of epikeratophakia and keratoprostheses treatment for corneal disorders.............................	1,500	7,000
Surgical vs. laser management of advanced glaucoma.......................	1,000	5,000
Subtotal, NEI....................	8,000	37,000
NIAMSD:		
Epidermolysis bullosa: efficacy of dilantin and treatment of esophageal strictures.............................	500	2,500
Efficacy of 13-cis retinoic acid in treating keratinizing disorders..........	1,000	3,000
Subtotal, NIAMSD.................	1,500	5,500
TOTAL, NIH......................	79,054	360,937

INCREASED RATE OF DOWNWARD NEGOTIATIONS

Mr. Roybal. What is the research community, particularly grantees with projects already under way, telling you about the kinds of adjustments they will have to make in their research plans and protocols to accommodate a downward negotiation of 6 percent in FY 1986 and 11 percent in FY 1987 from study section recommended amounts?

Dr. Wyngaarden. Most investigators would need to reduce support and professional staffs and to forego expenditures for equipment, supplies, travel. In some cases, it may be necessary to decrease the numbers of human subjects or experimental animals that could be handled.

RECRUITING AND RETAINING STAFF

Mr. Roybal. What evidence can you provide that problems such as Administration efforts to cut intramural funding, periodic hiring freezes, difficulty in keeping salaries competitive, operational changes to absorb Gramm-Rudman-Hollings reductions, and greater involvement of OMB in the operation of the agency has or has not made it more difficult for NIH to recruit and retain the very best scientists?

Dr. Wyngaarden. For some time, the recruitment and retention of scientific staff have represented a problem to the NIH and, indeed, the entire Federal Government. We cannot state with certainty what the precise impact on recruitment and retention rates will be as a result of the recent austerity policies.

AFFIRMATIVE ACTION

Mr. Roybal. In response to the GAO finding that the National Institutes of Health does not meet Federal affirmative action requirements, and that Hispanics particularly are under-represented in most occupational categories according to HHS's own criteria, what corrective actions does NIH plan to undertake?

Dr. Wyngaarden. The NIH was found not to be in full compliance four of eight Federal requirements for affirmative action. These four requirements are listed below, as are the corrective actions that will be undertaken to fully meet affirmative action requirements:

--Establish numerical hiring goals:

> The Director, NIH, has appointed a committee to develop methodology for establishing meaningful goals that will meet the EEOC requirements. Once goals are established, this committee will develop a mechanism for implementation of these goals within the NIH. To augment the committee's actions, the NIH Division of Equal Opportunity (DEO) has already investigated the use of automated systems for the calculation of goals and manipulation of data for meeting affirmative action requirements and has proceeded with preparing the documentation required to purchase the necessary computer hardware and software packages.

--Develop and implement minority and female recruitment plans in those organizational components that do not have them:

The Director, NIH, plans to direct the five components that do not have minority and female recruitment plans to prepare and submit them to the DEO. It should be noted that the Office of the Director (OD) Personnel Office has already begun the development of an Affirmative Action Program (AAP/Federal Equal Opportunity Recruitment Program (FEORP) plan for the Office of the Director and the Office of Research Services. The National Library of Medicine has also begun the development of a FEORP plan for minorities and women.

--Identify and eliminate employment barriers for minorities:

NIH has conducted barrier analyses in accordance with the Public Health Service guidance on AAP/FEORP. Analyses of four series have been completed at NIH. It is anticipated that analyses of the remaining target series will be completed before the end of FY 1986. Should any barriers to equal employment opportunities be found, NIH will take appropriate actions to correct the situation.

It should also be noted that NIH participated in the development of the methodology for a PHS-wide study on barriers to the employment of Hispanics and native Americans, conducted a barrier analysis in NIH component organizations, and participated in analyzing data and writing the PHS final report issued in September 1984.

Since that time, NIH has implemented several of the recommendations contained in the PHS report.

--Collect data on the race, ethnic origin and gender of job applicants to monitor and evaluate the effectiveness of affirmative action efforts:

The NIH discontinued collecting data on the race, ethnic origin, and gender of job applicants based on instructions received from the U.S. Office of Personnel Management (OPM). The OPM issued a letter in December 1983 indicating that these data should no longer be collected because the Office of Management and Budget authorization to use the OPM Form 1386, Background Survey Questionnaire, had expired. As pointed out in the GAO report, the NIH, as well as other Federal agencies, is required by Equal Employment Opportunity Commission (EEOC) regulations to collect data on applicants, but is caught in a bind between EEOC and OPM, who allowed OPM Form 1386 to expire without seeking its reauthorization.

The NIH, in April 1984, sought guidance on this issue from the Department of Health and Human Services, which in turn sought guidance from the U.S. Office of Personnel Management. The DHHS was unable to resolve this matter with

> OPM. Until this issue is resolved, NIH will be unable to meet this affirmative action requirement. The inability to collect these data also impacts on the "adequacy" of barrier analyses being conducted by the NIH.

Mr. Roybal. Is NIH hampered in collecting data on the race, ethnic origin, and gender of job applicants, which is critical to monitoring and evaluating the effectiveness of its affirmative action program, by the lack of OMB authorization to use the instrument used government-wide to collect these data?

Dr. Wyngaarden. As explained above, the NIH is hampered in collecting data on the race, ethnic origin, and gender of job applicants because of the lack of OMB authorization to use OPM Form 1386, Background Survey Questionnaire.

Mr. Roybal. What is the current representation of Hispanics, blacks, other major minority groups, and women in NIH's overall workforce, and in all occupation and grade-level categories? (Please supply numbers and percentages.)

Dr. Wyngaarden. The requested information has been compiled and will be provided to the Subcommittee. The volume of data (330 pages) precludes its practical insertion in the hearing record.

AFFIRMATIVE ACTION

Mr. Stokes. During fiscal years 1982-1984, NIH took longer to render decisions on and resolve complaints after receiving investigation reports from the Department of Health and Human Services than any other component of the Public Health Service, and the median time increased from 230 days to nearly 400 days. These long delays also contribute apparently to the perception of many employee groups, Dr. Wyngaarden, that you are not committed to equal employment opportunity. Why does it take so long to process discrimination complaints at NIH?

Dr. Wyngaarden. Problems associated with the length of time taken to process complaints of discrimination during fiscal years 1982-1984 resulted from a combination of factors: the lack of an experienced manager within the complaints branch in the NIH Division of Equal Opportunity; the long-standing practice of contracting out the preparation of complaints of discrimination, which resulted in limited controls on the quality of reports, requiring extensive revisions by the NIH; and inadequate staff resources in the NIH DEO. These problems were remedied during fiscal years 1984 and 1985, as noted in the GAO report.

Mr. Stokes. What are you doing to improve the situation?

Dr. Wyngaarden. Several actions have been taken to improve the timeliness of processing complaints of discrimination. The new Director of DEO appointed a new manager of the division's complaints branch; discontinued contracting to have disposition reports prepared; employed a private consultant to train division staff in preparing disposition reports; hired additional support staff; and has held regular meetings with EEO officers representing the various NIH components.

These activities resulted in the issuance of 41 proposed dispositions between December 1984 and August 1985 and elimination of the backlogged cases over which the division had control. In addition, the processing time for complaints has dropped from 395.5 days in FY 1984 to 137 days in FY 1986. The elimination of the backlog and improved processing time has allowed staff to process complaints in the established DHHS timeframes, as well as time to address other areas involved with complaints processing; e.g., providing appropriate BID staff with relevant information concerning complaints in their BIDs.

ADVISORY COMMITTEES

Mr. Stokes. Please describe the role of the various NIH advisory committees.

Dr. Wyngaarden. The public advisory committees of the NIH can be divided into four categories:

(1) Technical and scientific peer review committees, which provide initial review of grant and cooperative agreement applications and contract proposals;

(2) Boards of scientific counselors, which provide outside peer review of the scientists and the research performed in NIH laboratories;

(3) Program advisory committees, which review and recommend on the direction of research under consideration by each Bureau, Institute, or Division of the NIH; and

(4) National advisory councils and boards, which provide the second level of peer review for grant and cooperative agreement applications, and consider the recommendations of the boards of scientific counselors regarding research conducted at the NIH. Councils and boards also advise and recommend on program and policy issues relevant to the missions of the Institutes they serve.

Mr. Stokes. How many such committees exist?

Dr. Wyngaarden. Of the 150 public advisory committees at NIH, 106 are technical and scientific peer review groups; 14 are boards of scientific counselors; 16 are program advisory committees; and 14 are national advisory councils and boards.

Mr. Stokes. According to the General Accounting Office, the number of blacks serving on NIH Public Advisory Committees was 99 in 1979. This number increased to 116 in 1981 but declined to 95 by 1984. Meanwhile, the number of non-minorities increased by 304. Please provide for the record the current number of all persons serving on NIH Public Advisory Committees and the breakdown for women, blacks, Asians, native Americans, and non-minorities.

Dr. Wyngaarden. As of December 31, 1985, there were 2,471 persons serving on all NIH public advisory committees, including 494 women, 98 blacks, 198 Asians, 14 native Americans, 75 Hispanics, and 2,086 non-minorities.

Mr. Stokes. What steps is the NIH taking to increase the number of blacks appointed to NIH Public Advisory Committees?

Dr. Wyngaarden. It has been the policy of the NIH since 1978 that there must be at least one female and one minority candidate on each slate of nominees forwarded for the 150 public advisory committees. There has been renewed emphasis on the consideration and nomination of blacks as a result of an internal study completed in 1985 on the participation of minorities and women on NIH public advisory committees. Officials of the NIH have alerted staff to actively search for qualified blacks and other minorities and women for such service.

The report of the study included other recommendations: 1) select women and minority (especially black) candidates first when developing a slate of nominees; 2) seek potential women and minority advisors when visiting institutions and organizations, and when attending professional meetings; 3) use women and minorities as ad hoc reviewers, leading toward membership on NIH committees; and 4) continue to train young women and minorities who are interested in establishing themselves as research scientists.

Data gathered by independent organizations, such as the American Association Medical Colleges and the National Research Council, show that more women and minorities who have attained doctoral degrees are being hired by medical schools. It is assumed that a number of these individuals will select medical research as a career and will therefore be available in the future for appointment to NIH committees.

Efforts will be continued to appoint women and minorities, especially blacks, to NIH public advisory committees.

PROPOSED RESCISSIONS

Mr. Early. Under the March sequestration order, the FY 1986 enacted appropriation for NIH will be reduced by 4.3 percent or $236.2 million. In addition, the Administration is also proposing a further decrease in funds--a rescission of $76.782 million. Doctor, why is this rescission being proposed? Won't the Gramm-Rudman reduction cause sufficient damage to NIH programs?

Dr. Wyngaarden. The FY 1987 policy of stabilizing research project grant funding at 18,000 grants and the desirability of providing a smooth transition from FY 1985 through FY 1987 form the basis for the proposal to rescind $53.7 million and 581 competing research project grants in FY 1986. The number of competing awards in FY 1986 was reduced in order to achieve the 18,000 stabilization objective without drastically reducing the number of competing research project grants in FY 1987.

The decision to propose rescinding $13.9 million associated with AIDS research was based on the fact that Congress provided NIH $20.0 million more in the FY 1986 appropriation than NIH had previously identified in the FY 1986 proposed budget amendment for AIDS research. The proposed budget amendment, which included an increase of approximately $50.0 million over the FY 1986 request for NIH, reflected the best current estimate of NIH requirements to fund the continuing and new research initiatives for the treatment and prevention of this disease.

A rescission of approximately $9.1 million is proposed from the small and minority universities and colleges program. The Congress provided $20.0 million for this program in the FY 1986 appropriation, an increase of $10.0 million over both the FY 1985 funding level and the FY 1986 request. Given the need to reduce Federal expenditures because of the growing deficit, the Administration believed that such a significant add-on was unnecessary for a new program begun in FY 1985 with an initial appropriation of $10.0 million.

Mr. Early. How was the discussion arrived at to propose a rescission of NIH funds on top of the Gramm-Rudman cut? I wouldn't think that you heartily or even half-heartedly endorse this reduction.

Dr. Wyngaarden. In order to submit a 1987 budget that conformed with the deficit target in the Balanced Budget and Emergency Control Act, the 1986 appropriation was revised by OMB and reductions proposed. In other words, it was necessary to take a second look at the FY 1986 appropriation for proposed reductions that would not seriously undermine the strength of the biomedical research program and that would help ameliorate the effect of the reduced level of the FY 1987 request. For example, the FY 1986 research project grant proposed rescission of $53.7 million and 581 competing awards was predicated on the desire to avoid a grant fluctuation in the funding of competing research project grants from FY 1986 to FY 1987, and to have a smooth transition to the Administration's stabilization policy of funding 18,000 total research project grants.

Mr. Early. How was the amount of the rescission determined? Were you assigned a target figure by OMB? HHS?

Dr. Wyngaarden. The final rescission amount was computed by applying the OMB overall policy directives, which set both the total number of research project grants in FY 1986 and the change in the aggregate average cost of NIH research project grants for FY 1987 over FY 1986.

Mr. Early. Was NIH and each Institute given the flexibility to determine in which research mechanisms to take these rescissions? Or were you directed by OMB, or OMB acting through the Department, to take the rescission in these areas? Were you told to take them in these areas?

Dr. Wyngaarden. The NIH did not have flexibility regarding the rescission proposed in the research project grants mechanism or in the level for AIDS research. The rescission in the small universities and colleges program was proposed by NIH as a means of meeting overall NIH budget targets for FY 1986. In each case, these were programs for which the FY 1986 appropriation provided additional funds over the request.

Mr. Early. Doctor, were you directed to take a specific amount of the rescission in new and competing research grants?

Dr. Wyngaarden. The specific amount of the FY 1986 rescission in competing research project grants was calculated by applying OMB overall policies regarding both the total number of research project grants and the aggregate average costs of those grants in order to have a smooth transition to 1987.

Mr. Early. Would you explain to me how NIH lost an additional $32 million to rescissions between the early part of January and the time the budget request was submitted? I understand that not only did you end up with a larger rescission, but that rescissions are being proposed in more Institutes. Please explain how this came about.

Dr. Wyngaarden. The decision during January to increase the FY 1986 rescission for research project grants by an additional $32.0 million was necessary to comply with OMB directives regarding the aggregate average costs of grants in FY 1986 and FY 1987. This further reduction in FY 1986 was required to assure that the aggregate average costs of research project grants in FY 1987 would show an increase of 2 percent over comparable FY 1986 levels before the proposed indirect cost reduction was taken into account.

Mr. Early. Doctor, what impact will combined reductions of Gramm-Rudman and the proposed rescissions have on NIH research programs and on the quality of research? Will any new or on-going research initiatives be lost, halted, or delayed?

Dr. Wyngaarden. The FY 1986 revised budget will fund a total of 18,195 research project grants, a decrease of 162 grants below the FY 1985 level of 18,357 and 581 below the FY 1986 appropriated level. The resources provided will permit an increase of approximately 4.5 percent in the aggregate average cost of NIH research grants. At this level, downward negotiations averaging about 6.5 percent will be imposed from the full study section recommended amounts for competing awards and committed levels for noncompeting continuations. Historical negotiations have averaged 3 percent for competing and 1 percent for noncompeting.

The number of research trainees will be decreased to approximately 9,950, a reduction of about 400 trainees from the FY 1986 appropriated level and 700 trainees from the FY 1985 level.

All other NIH research mechanisms will, at the aggregate level, be supported at the FY 1986 appropriated level less the 4.3 percent reductions imposed by sequestration.

While the proposed reductions will certainly affect the amount of research that NIH can support, we do not expect to compromise the quality of research to be conducted. We will support the very best science and our highest priority research areas. The reductions will slow the pace of some ongoing initiatives, and will delay implementation of some new ones. However, we will continue to maintain a strong biomedical research program.

Mr. Early. Did you have any opportunity to appeal the proposal to rescind funds? Did the Department appeal this further cut?

Dr. Wyngaarden. Both the NIH and the Office of the Secretary, DHHS, appealed the initial FY 1986 levels proposed by the OMB.

BUDGET REQUEST

Mr. Early. Will you describe the process used to determine the FY 1987 budget request for NIH?

Dr. Wyngaarden. The development of the FY 1987 request for NIH evolved in five stages: 1) the Institutes' requests to NIH; 2) the NIH request to PHS; 3) the PHS request to DHHS; 4) the DHHS request to OMB; and 5) the OMB passback, which finalized the request sent to Congress. In a break with the past, the NIH FY 1987 requests to PHS and DHHS were submitted by mechanism rather than by Institute. This change was necessary because of the uncertain status of the FY 1985 budget with regard to the then-unresolved multiyear funding issue and its impact on the FY 1986 request.

As usual, the NIH submissions were reviewed for the following: adherence to policy; accuracy; the strength of the justifications for ongoing and new programs such as the low birth weight initiative; and the inclusion of proposed amendments in FY 1986 for such areas as AIDS research and pertussis vaccine development. At each stage, the NIH was provided an opportunity to appeal initial budget decisions reflected in the allowance.

In general, this cycle typifies the yearly NIH budget formulation process.

Mr. Early. Doctor, did NIH receive any specific instructions as to the content of the request that should be sent forward to PHS/HHS?

Were you given a limit, either in terms of numbers or dollars, on what you could propose for total research grants? New and competing grants or centers?

Dr. Wyngaarden. Each year, the PHS provides NIH with technical instructions for the development of the preliminary submissions. Specifically, the PHS guidance stated that the FY 1987 submission should be predicated on the estimates and policies reflected in the FY 1986 President's budget. In addition, NIH was instructed to use the OMB factor of 4.2 percent for inflationary cost increases.

The PHS did require the preliminary budget to be submitted at several funding levels, one of which was the FY 1987 target included in the FY 1986 President's budget. The NIH was permitted to submit a level reflecting its priorities and judgments; i.e., no constraints on the total number of research project grants, number of competing research project grants, or centers.

After review by the PHS, NIH received guidance on the funding levels to be requested of HHS. These represented the views of the Assistant Secretary for Health after considering all the priorities of the various PHS agencies.

STABILIZATION POLICY

Mr. Early. The budget indicates that the Administration is proposing a "new stabilization policy" regarding NIH funding of research project grants by "stabilizing" the total number of grants at 18,000. Why this change in thrust, Doctor?

Dr. Wyngaarden. The requirement to reduce the growing Federal deficit has forced the Administration to focus greater attention on out-year commitments resulting from current year discussions; for example, the number of new and competing research project grants. In addition, in the context of limited fiscal resources, it was also necessary to examine the impact of research project grants support on the balance of other NIH funding mechanisms.

Mr. Early. How was the 18,000 figure arrived at? Is it just coincidence, Doctor, that this results in 5,100 new and competing grants--100 grants more than under the Administration's "old policy" of 5,000 new and competing grants?

Dr. Wyngaarden. The 18,000 figure was based on two considerations. First, it was developed after a review of historical data indicating a steady increase in the total number of grants from 16,198 in FY 1980 to 18,357 in FY 1985 and with consideration of the impact of continued growth of this activity. Second, it was considered by OMB to be consistent with the Senate leadership-White House agreement, in developing the FY 1986 budget, to fund 6,000 (average 3-year) new and competing grants per year.

Mr. Early. In FY 1985 we funded 6,246 competing grants; under the FY 1986 bill 6,100. You indicated that you will fund 6,100 after sequestration. Why not 6,100 or 6,200 in FY 1987?

Dr. Wyngaarden. Within the 1987 President's budget level, the funding of 6,100 or 6,200 new and competing project grants would not be possible without further reducing the average cost or seriously undermining the funding of other mechanisms and, therefore, NIH's program balance. For this reason, the Administration is proposing a new stabilization policy for research project grants at 18,000 total grants.

Mr. Early. Was this primarily a "budget" decision or one based on the scientific opportunities available?

Dr. Wyngaarden. The decision to fund 18,000 grants was both a budget decision based on consideration of deficit reduction targets for FY 1987 and succeeding years and a programmatic decision to move away from the new and competing grant target.

Mr. Early. To what extent was NIH involved in developing this "new policy"?

Dr. Wyngaarden. Although NIH was not involved in the development of the new stabilization policy, the policy was discussed at the time of the OMB passback, and our views were considered at that time. The Department did not appeal the new stabilization policy.

Mr. Early. Doctor, were you permitted to take an appeal to OMB on this budget request?

Dr. Wyngaarden. The NIH does not appeal directly to OMB. The NIH submits its appeals to the Assistant Secretary for Health, who reviews them in the context of the total PHS and forwards to the Department those he approves. The Secretary reviews the appeals from all the agencies of the Department and then sends those he approves to the OMB.

PAYLINES AND AWARD RATES

Mr. Early. To what payline will you fund under the revised FY 1986 and the FY 1987 request? What's the range of paylines? How does this compare to FY 1985 and the FY 1986 enacted appropriation bill?

Dr. Wyngaarden. The listing below displays the range of paylines and the NIH average payline for FY 1985, the FY 1986 appropriation, the FY 1986 revised estimate, and the FY 1987 request.

	Range of Paylines	Average Payline
1987 Request	140-190	160
1986 Revised Estimate	150-220	160
1986 Appropriation	160-220	170
1985 Actual	157-203	172

Mr. Early. What percentage of grants will you fund under the revised FY 1986 and FY 1987 budget estimates? What's the percentage range? How does this compare to FY 1985 and FY 1986 appropriation bill level?

Dr. Wyngaarden. Shown on the following page are the range of award rates and the NIH average for FY 1985, the FY 1986 appropriation, the FY 1986 revised estimate, and the FY 1987 request.

	Range of Award Rates	Average Award Rate
1987 Request	22.2 - 35.8%	27.4%
1986 Revised Estimate	26.5 - 50.4%	30.7%
1986 Appropriation	27.4 - 54.5%	33.9%
1985 Actual	28.2 - 49.2%	37.3%

RESEARCH PROJECT GRANTS

Mr. Early. Doctor, not only are you proposing to fund 1,000 fewer grants than provided for in the FY 1985 bill, but the number of grants you propose to fund in FY 1986 and FY 1987 is also less than that for FY 1985 and FY 1983. Why is that?

Dr. Wyngaarden. The requirement to reduce the growing Federal deficit has forced the Administration to focus attention not only on current year decisions but also on the out-year commitments of those decisions. In addition, in the context of limited fiscal resources, it was necessary to examine the impact of research project grants support on the other NIH funding mechanisms. To continue the FY 1985 funding policy of awarding 6,100 competing grants in FY 1986 and FY 1987 would result in a total of over 19,000 research project grants in FY 1987. During a period of fiscal restraint, this level of support could not be sustained without compromising the other NIH research funding mechanisms.

Mr. Early. Did this decision have anything to do with the merit or level of research opportunities out there today?

Dr. Wyngaarden. The decision to fund fewer new and competing grants in FY 1986 and FY 1987 was not based on a decline in scientific merit of applications received or the levels of research opportunities. The primary concern in reaching this decision was based on the level of resources available, and the need to maintain program balance.

Mr. Early. Doctor, aren't you going in the wrong direction? I thought we were supposed to progress, not retrogress.

Dr. Wyngaarden. Investigator-initiated research continues to be the highest priority of NIH since it provides the impetus for the medical advances of the future. The funding of 18,195 research project grants in FY 1986 and 18,000 in FY 1987 will enable NIH to continue to support a strong program of biomedical research.

Mr. Early. Please provide for the record a table displaying, by Institute, the number of new and competing grants, the paylines, and the award rates for FY 1985, the FY 1986 appropriation level, the FY 1986 revised estimate, and the FY 1987 request.

Dr. Wyngaarden. The tables on the following two pages provide the requested information.

DIRECT COSTS

Mr. Early. The conference report accompanying the FY 1986 bill expressed some concern about the increases in the direct costs of

DHHS-NATIONAL INSTITUTES OF HEALTH

COMPETING RESEARCH PROJECT GRANTS-APPLICATIONS FUNDED

(Dollars in thousands)

	FY 1985 ACTUAL 1/				FY 1986 APPROPRIATION				FY 1986 APPROPRIATION AFTER SESQUESTRATION			
	NUMBER	AMOUNT	PAYLINES	AWARD RATE	NUMBER	AMOUNT	PAYLINES	AWARD RATE	NUMBER	AMOUNT	PAYLINES	AWARD RATE
NCI	1017	$168,464	172	36.4%	931	$175,7)7	170	29.9%	931	$168,312	170	29.9%
NHLBI	901	158,203	177	36.8	886	162,378	190	35.1	886	155,423	190	35.1
NIDR	131	15,859	195	41.2	149	18,083	220	42.8	149	17,309	220	42.8
NIADDK	786	104,756	173	35.1	637	96,949	170	35.0	637	93,212	170	34.1
NINCDS	722	105,978	157	37.8	646	105,159	150	28.9	646	100,637	150	28.9
NIAID	549	72,045	159	36.5	527	77,168	160	32.6	527	73,874	160	32.6
NIGMS	987	133,845	165	44.8	972	138,792	160	41.6	972	132,874	160	41.6
NICHD	469	64,200	162	28.2	483	67,668	170	27.4	483	64,779	170	27.4
NEI	367	47,230	198	49.2	358	47,066	210	54.5	358	45,046	210	54.5
NIEHS	108	16,624	203	32.3	111	16,931	200	30.6	111	16,203	200	30.6
NIA	209	30,895	202	34.3	201	32,442	210	34.5	201	31,104	210	34.5
NIAMSD	--	---	--	--	199	27,611	170	31.7	199	26,130	170	31.7
TOTAL NIH	6,246	918,099	172	37.3	6100	965,954	170	33.9	6100	924,903	170	33.9

COMPETING RESEARCH PROJECT GRANTS-APPLICATIONS FUNDED - cont'd.

(Dollars in thousands)

	FY 1986 ESTIMATE				FY 1987 REQUEST 2/			
	NUMBER	AMOUNT	PAYLINES	AWARD RATE	NUMBER	AMOUNT	PAYLINES	AWARD RATE
NCI	857	$161,512	160	27.5%	874	$149,070	160	26.8%
NHLBI	817	143,954	180	32.4	802	145,635	180	29.9
NIDR	149	17,309	220	42.8	110	12,683	190	31.3
NIADDK	564	86,756	160	31.0	566	82,627	160	22.2
NINCDS	598	91,083	150	26.7	538	80,126	140	22.5
NIAID	465	70,770	150	28.8	421	58,126	150	26.7
NIGMS	810	124,359	160	34.7	689	100,867	150	30.7
NICHD	467	64,379	170	26.5	456	62,826	160	24.6
NEI	331	41,856	200	50.4	250	33,869	170	35.8
NIEHS	111	16,203	200	30.6	105	15,301	190	25.2
NIA	177	28,425	200	30.4	145	23,502	190	25.0
NIAMS	173	24,606	160	27.5	148	19,909	160	22.6
TOTAL NIH	5519	871,212	160	30.7	5104	784,541	160	27.4

NOTE: Paylines for actual years represent the 90th percentile priority score, based on the number of funded research projects. Paylines for estimated years represent the 100th percentile priority score.

All 1986 columns reflect carryover.

1/ NHLBI and NICHD use percentiles for making funding decisions and the priority scores shown are derived from the percentile score listings in an analogous manner.

2/ Reflects consolidation of AIDS in DASH, all other columns include funds for AIDS.

research. Doctor, would you explain to us what accounts for these increases? Does it have anything to do with the fact that priority scores are contracting?

Dr. Wyngaarden. NIH has been reviewing the escalation over the last 5 years of the costs associated with traditional research project grants (R01s). While our analysis, the results of which are still preliminary, has proven inconclusive on some points, NIH has been able to narrow down the major reasons for the growth in the average total cost.

The principal factors responsible for this increase are the growth of indirect costs, which have increased by about 63 percent in the last 5 years, and the personnel costs associated with direct costs, which account for about 66 percent of the growth in direct costs of R01s over the last 5 years.

The personnel costs component of R01 direct costs has risen at a greater rate than other direct costs in spite of an apparent slight decline in the compensated effort of Principal Investigators (PIs) and non-doctorate research staff. Doctorate-level staff, however, are now being compensated for a larger fraction of their time.

In addition, it was observed that:

- o More PIs are charging salary against the research project grant (22.4 percent of PIs in FY 1981 charged no salary, compared with only 19.0 percent in FY 1985);
- o More doctorate-level staff are charging salary on research project grants (98.5 percent in FY 1985; 57.6 percent in FY 1981);
- o Non-doctorate staff are also less frequently listed as providing free service to the research project (0.2 percent in FY 1985; 6.4 percent in FY 1981);
- o PI compensation increased 34.3 percent in 4 years; other doctorate-level staff compensation increased 17.7 percent per person; and non-doctorate staff compensation increased 12.4 percent per person.

All these are preliminary observations based on limited studies and require further detailed analyses and confirmation.

In NIH's review of the "whys" of the growth of direct costs over the last 5 years, other reasons have been suggested, but are inconclusive. For example, one such hypothesis suggested that the costs of some scientific techniques have risen faster than others. Another observation states that projects involving human research subjects may have increased in average cost more than projects not involving human subjects.

Yet to be determined are the influences of new methods of biotechnology, non-reusable research materials, improved animal strains, new animal care guidelines, and other changing features of modern biological science.

With regard to priority scores, it was observed that study sections find less fault and recommend smaller cost reductions on better applications. As the payline has fallen in recent years, the proportion of such grants among all awards has risen; therefore, the average cost of all awards has also risen.

Mr. Early. While the report states that the Department and NIH should take steps to restrain these increases, it also states that "arbitrary percentage reductions...should not substitute for careful management ." Has NIH begun to review this matter, and what are your plans with respect to this matter?

Dr. Wyngaarden. The NIH continues to review the matter of average cost growth.

The FY 1986 revised budget request would require downward negotiations from full study section recommended levels of 6.7 percent for competing awards and 6.5 percent for noncompeting continuations. It is expected that some of the reduction will be achieved through developing greater efficiencies, especially in the areas of personnel and the purchase of supplies and equipment. It would be our intention that all these reductions be achieved through careful management. However, given levels of negotiations of this magnitude, some research project grants can be expected to be scaled back from what was approved by peer review. These reductions would be achieved on an individual basis after careful consideration by the Institute supporting that particular grant.

DOWNWARD NEGOTIATIONS

Mr. Early. The justification indicates that, under the FY 1986 revised estimate, one way NIH will accommodate the proposed reduction is through downward negotiations averaging 6 percent from study section recommendations for competing awards and committed levels for noncompeting continuations. Is this the main reason for this downward negotiation proposal? How were the percentage reductions determined? Are they going to be the arbitrary types of reductions the conferees counseled against?

Dr. Wyngaarden. The level of downward negotiations is due, primarily, to an effort to meet the funding reductions that are to be implemented under the FY 1986 revised estimate. The percentage reductions were determined based on the availability of funds to support investigator-initiated research and the number of grants to be supported at this funding level. It is expected that some of the reduction will be achieved through developing greater efficiency, especially in the area of personnel and in the purchase of supplies and equipment. In addition, some research projects will be reduced in scope. The reductions will not be taken across-the-board.

Mr. Early. Are downward negotiations assumed for mechanisms other than research grant awards? How much to you expect to "save" in FY 1986 as a result of this proposal?

Dr. Wyngaarden. The FY 1986 revised estimate assumes downward negotiations in the research centers mechanism of each NIH Institute and in the other research grant mechanisms of the NCI, NINCDS, and

DRR. The rate of these negotiations and the amount of savings are as follows:

Downward Negotiations in Centers
(Dollars in Thousands)

	FY 1986 Revised	
	Average Downward Negotiation	Amount of Savings
NCI....................	10.0%	$9,126
NHLBI..................	10.0	9,202
NIDR...................	15.2	2,385
NIDDK..................	13.0	3,627
NINCDS.................	4.0	1,202
NIAID..................	7.0	418
NIGMS..................	8.0	850
NICHD..................	12.0	3,594
NEI....................	11.6	842
NIEHS..................	4.3	662
NIA....................	19.0	2,334
NIAMSD.................	13.0	1,463
DRR....................	7.9	12,795
FIC....................	4.3	86
Total, NIH......	10.6	48,586

Downward Negotiations in Other Mechanisms
(Dollars in Thousands)

	FY 1986 Revised	
	Average Downward Negotiation	Amount of Savings
NCI:		
Organs Systems.................	4.3%	$43
Clinical Education.............	9.0	445
Cooperative Clinical Groups....	8.5	4,463
NINCDS:		
Cooperative Clinical Groups....	4.3	43
DRR:		
Minority Biomedical Research Support.......................	4.6	1,151
Total, NIH...............		6,145

Mr. Early. The FY 1987 request assumes even greater downward negotiations in direct costs--approximately 11 percent on average. Why is such a large reduction being proposed? What are the estimated savings?

Dr. Wyngaarden. The FY 1987 request provides support for 17,889 total research project grants at a level that reflects downward negotiation of direct costs from commitment or recommended levels of approximately 11 percent. This represents an additional downward negotiation of about 9 percent from historical funding levels. Compared to the 1986 average grant size, for direct costs the request reflects a 2 percent increase. These large downward negotiations are a result of major increases in the estimated recommended level of support for these grants. In response to Congressional concerns, we are increasing our cost consciousness as will make selective reductions to these recommended levels. Given limited resources, it is not in the best interest of biomedical research to fund approximate full costs for research project grants at the expense of other mechanisms. Estimated savings of direct costs resulting from this funding policy are approximately $293 million. These savings are in addition to the estimated indirect cost savings of $72 million in research project grants.

Mr. Early. I always thought that a grant in noncompeting continuation status was in "full swing," so to speak. Doctor, are you at all concerned about the effect these large direct cost cuts have on the ability of researchers to carry out their projects? On the quality of the research?

Dr. Wyngaarden. Yes, we are concerned with these cuts; however, in these times of fiscal constraints all programs must participate. While the cuts will require some reduction in research scope, we will maintain the quality of research.

REDUCTION IN GRANT COSTS

Mr. Early. Please provide for the record a breakdown for each Institute, by mechanism, of the percentage reduction, indirect costs, and the associated savings under the FY 1986 bill level, the FY 1986 revised request, and the FY 1987 request.

Dr. Wyngaarden. The tables on the following four pages show the amount of savings derived through downward negotiations by mechanism for the FY 1986 appropriation, the FY 1986 revised estimate, and the FY 1987 request levels. The last table provides the savings in FY 1987 associated with the proposed indirect cost reduction. The proposed indirect cost reduction has no impact on FY 1986; therefore, no savings are estimated for these levels.

COMPETING RESEARCH PROJECT GRANTS

Mr. Early. Doctor, how many competing grants could be funded in FY 1987 if direct costs were funded at historical levels? With the direct cost reduction assumed in the FY 1986 revised request?

Dr. Wyngaarden. Assuming the FY 1987 total dollar level, if direct costs for both noncompeting and competing grants were funded at historical levels, NIH could support about 3,400 to 3,500 competing awards.

If direct costs were funded in FY 1987 at the same levels assumed in the FY 1986 revised request, NIH could support about 4,350 to 4,450 competing awards.

DHHS - National Institutes of Health

Research Project Grants

SAVINGS DERIVED FROM DOWNWARD NEGOTIATIONS

(Dollars in thousands)

	1986 Appropriation		1986 Revised Estimate		1987 Request	
	Amount	% Negot.	Amount	% Negot.	Amount	% Negot.
NCI................	$6,033	1.0%	$23,371	4.1%	$46,750	7.9%
NHLBI..............	4,910	0.9	26,972	5.1	55,681	9.8
NIDR...............	759	1.6	2,777	5.8	3,579	7.2
NIDDKD.............	14,896	3.6	25,784	6.5	34,155	10.3
NINCDS.............	---	---	15,089	5.3	40,280	12.7
NIAID..............	5,143	2.0	9,280	3.7	23,767	9.1
NIGMS..............	5,268	1.2	11,030	2.7	34,835	7.9
NICHD..............	5,766	2.8	15,200	7.5	17,046	8.1
NEI................	6,814	4.4	15,530	10.2	16,185	10.4
NIEHS..............	1,194	2.1	3,606	6.3	3,522	6.1
NIA................	---	---	1,889	2.2	7,178	7.7
NIAMSD.............	---	---	---	---	10,289	11.9
TOTAL...........	50,783	1.6	150,528	5.0	293,267	9.3

NOTE: The dollar savings have been adjusted to reflect the historial negotiations of 3 percent in competing and 1 percent in noncompeting.

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Research Centers

SAVINGS DERIVED FROM DOWNWARD NEGOTIATIONS
(Dollars in thousands)

	1986 Appropriation		1986 Revised Estimate		1987 Request	
	Amount	% Negot.	Amount	% Negot.	Amount	% Negot.
NCI................	$5,435	6.0	$9,126	10.0	$7,104	7.9
NHLBI..............	5,481	6.0	9,202	10.0	14,626	16.2
NIDR...............	1,787	11.4	2,385	15.2	2,115	15.2
NIDDKD.............	2,535	9.1	3,627	13.0	7,741	24.5
NINCDS.............	---	---	1,297	4.3	5,045	29.8
NIAID..............	168	2.8	418	7.0	1,587	13.0
NIGMS..............	411	3.9	850	8.0	979	16.3
NICHD..............	2,411	8.1	3,594	12.0	5,103	19.4
NEI................	580	8.7	842	11.6	1,299	9.6
NIEHS..............	---	---	662	4.3	1,538	9.4
NIA................	1,887	15.4	2,334	19.0	1,021	17.5
NIAMSD.............	1,024	9.1	1,463	13.0	1,953	9.0
DRR................	6,093	3.8	12,795	7.9	15,505	---
FIC................	---	---	86	4.3	---	---
TOTAL..............	27,812	5.4	48,681	10.5	65,616	12.8

DHHS - National Institutes of Health

Other Research Grants

SAVINGS DERIVED FROM DOWNWARD NEGOTIATIONS
(Dollars in thousands)

	1986 Appropriation		1986 Revised Estimate		1987 Request	
	Amount	% Negot.	Amount	% Negot.	Amount	% Negot.
NCI:						
Organ Systems...............	---	---	$43	4.3	$396	33.1
Clinical Education..........	$293	4.9	445	9.0	390	14.0
Cooperative Clin. Groups....	1,854	3.6	4,463	8.5	1,370	2.7
NINCDS:						
Cooperative Clin. Groups....	---	---	43	4.3	85	8.2
DRR:						
Min. Bio. Rsch. Support.....	78	.3	1,151	4.6	1,926	7.4
Total, NIH...............	2,225	---	6,145	---	4,167	---

DHHS-National Institutes of Health

1987 INDIRECT COST SAVINGS BY MECHANISM
(Dollars in thousands)

	Research Project Grants	Research Centers	Other Research Grants	R&D Contracts	NCI Control Program	NLM	Total
NCI....................	$12,900	$390	$320	$725	$200	---	$14,535
NHLBI..................	11,853	2,022	280	1,400	---	---	15,555
NIDR...................	1,403	212	---	---	---	---	1,615
NIDDKD.................	7,519	656	35	71	---	---	8,281
NINCDS.................	6,993	658	---	254	---	---	7,905
NIAID..................	6,732	4	---	64	---	---	6,800
NIGMS..................	11,220	---	---	---	---	---	11,220
NICHD..................	4,380	670	---	475	---	---	5,525
NEI....................	3,485	170	---	85	---	---	3,740
NIEHS..................	1,442	509	---	89	---	---	2,040
NIA....................	2,285	10	---	---	---	---	2,295
NIAMSD.................	1,895	247	9	23	---	---	2,174
DRR....................	---	2,040	1,105	---	---	---	3,145
NLM....................	---	---	---	---	---	$170	170
TOTAL..............	72,107	7,588	1,749	3,186	200	170	85,000

CLINICAL TRIALS

Mr. Early. Clinical trials are funded in a variety of ways, including the research project grant and center mechanism. Are any of the clinical trials for which funds were provided in the FY 1986 bill not being funded because of the reductions required by the March 1 sequestration order?

Dr. Wyngaarden. As a result of sequestration, nine major new clinical trials will eliminated and seven others will be reduced in scope and funded at a lower level.

Mr. Early. Will you be able to continue the trials now underway at their planned levels?

Dr. Wyngaarden. In FY 1986, sequestration has reduced funds available for clinical trials in most Institutes. As a result, some modification to the scope and size of these trials may be required. We will of course make every effort to maintain the highest priority research at planned levels. The FY 1987 request provides approximately the 1986 sequester level of funding for clinical trials. To the extent that reductions from planned levels are necessary, we would, as in FY 1986, seek to maintain the highest priority trials at planned levels.

Mr. Early. Will you be precluded from initiating any new clinical trials because of the proposed rescissions?

Dr. Wyngaarden. As a result of the proposed rescissions in 1986, two major new clinical trials will be eliminated and one trial will be reduced in scope and funded for a lesser amount.

Mr. Early. Please provide for the record a list of the trials that fall into any of these categories.

Dr. Wyngaarden. The information follows.

MAJOR NEW CLINICAL TRIALS ELMININATED OR REDUCED AT
AT THE SEQUESTRATION LEVEL
(Dollars in Thousands)

NCI:	First Year Cost	Estimated Total Cost
Comparison of post operative radiotherapy and adjuvant chemotherapy with chemotherapy in children with medulloblastoma..	$100	$300
Phase I/II clinical trials of biological response modifiers......................	2,000	2,500
Treatment of carcinoma of the bladder with hematoprophyrin with photoradiation therapy..............................	70	210

NCI: (cont.)	First Year Cost	Estimated Total Cost
Use of TNF in patients with metastatic cancer who failed conventional therapy....	$1,150	$3,450
Study of radiolabeled monoclonal antibodies to detect Hodgkin's disease involvement..............................	182	546
Subtotal, NCI....................	3,502	7,006
NHLBI:		
Coronary artery bypass graft program........	850	29,500
Reduction in funds for cardiac A arrythemia treatment study................	150	---
Subtotal, NHLBI..................	1,000	29,500
NINCDS:		
Reduction in funds for 4 major trials from the appropriation level.	68	---
NICHD:		
Clinical trials within the Maternal-Fetal Medicine Network, including management of growth-retarded fetus, and management of pregnancies complicated by maternal diabetes and hypertension.................	500	2,500
Clinical trial within the Neonatal Intensive Care Units (NICUs) Network, including treatment for apnea of prematurity and the efficacy of home monitoring, management and preventive measures for necrotizing enterocolitis and examination of various available therapies for significant asphyzia during the perinatal and neonatal periods..........................	500	2,500
Reduction in funds for 2 major clinical trials from the appropriation level.......	30	---
Subtotal, NICHD..................	1,030	5,000
NEI:		
Reduction in funds for the diabetic macular edema study......................	100	---
TOTAL, NIH......................	5,700	41,506

ADDITIONAL MAJOR NEW CLINICAL TRIALS ELIMINATED OR REDUCED AT THE RESCISSION LEVEL

(Dollars in Thousands)

NIADDK:	First Year Cost	Estimated Total Cost
A multicenter study to test the safety and efficacy of treating lactic acidosis with dichloroacetate............	$470	$3,363
Effectiveness of diet therapy for prevention of progression of renal disease in children................................	354	730
Subtotal, NIADDK................	824	4,093

NEI:	First Year Cost	Estimated Total Cost
Reduction in funds for the diabetic macular edema study	50	---
TOTAL, NIH	874	4,093

Mr. Early. Doctor, does your FY 1987 budget request include funds for any new clinical trials? If so, please provide a list of these for the record, along with a brief description of each and the associated cost.

Dr. Wyngaarden. The 1987 request would support nine new clinical trials at a cost of $6.4 million. A listing of these trials follows:

MAJOR NEW CLINICAL TRIALS TO BE FUNDED AT 1987 REQUEST LEVEL
(Dollars in Thousands)

	First Year Cost	Estimated Total Cost
NCI:		
Comparison of bone marrow transplantation with chemotherapy for advanced stage neuroblastoma	$500	$1,500
Clinical trials using angiogenesis inhibitors	250	750
National collaborative diagnostic trials for staging and monitoring carcinoma of the prostate and lung	600	2,400
Phase III clinical trials in intraoperative radiotherapy for intra-abdominal malignancies	300	1,500
Phase II studies of adoptive immunotherapy of cancer with autologous LAK cells and IL-2	3,600	4,680
Treatment/imaging of lung cancer with a monoclonal antobody directed against bombesin/gastrin releasing hormone	488	1,464
Adoptive immunotherapy utilizing LAK cells and IL-2 administered intraperitoneally for patients with ovarian and colorectal cancer	172	516
Subtotal, NCI	5,910	12,810
NICHD:		
Studies on new long-acting injectable projestins	250	850
Comparison of effects of oral contraceptive use on physiological indicators of cardiovascular disease risk	200	1,200
Subtotal, NICHD	450	2,050
TOTAL, NIH	6,360	14,860

RESEARCH CENTERS

Mr. Early. The justification indicates that as a result of the March 1 sequestration order, there will be a decrease in the size and scope of research centers. Would you be more specific about what you mean by size and scope? How will all this be accomplished? Will both competing and noncompeting centers be affected? What is the percentage reduction in direct costs?

Dr. Wyngaarden. The level of funding for research centers will be reduced from full cost amounts and possibly, in some cases, from the levels provided in FY 1985. These reductions will require postponement of certain planned research activities and purchases of some supplies and equipment, thus reducing the amount of research to be conducted. It is expected that downward negotiations from full costs, averaging about 10.5 percent, will be applied against both noncompeting and competing centers. However, the Institutes will negotiate the funding level for each research center individually.

Mr. Early. The research centers program is scheduled for a further reduction in FY 1987--a decrease of 11 centers from the revised FY 1986 level of 534 and 13 centers from the FY 1986 bill level (536). Doctor, this wasn't you idea was it?

Dr. Wyngaarden. Within the amount of funds available in the FY 1987 request level, each NIH Institute and Division determined the number of research centers it could support. Consideration was given to individual research priorities and professional judgments as to the amount of reductions from full costs that could be imposed without seriously compromising the research conducted.

Mr. Early. Taken together, what effect will these reductions in the centers have on NIH's research program?

Dr. Wyngaarden. It is difficult to determine, at this time, the effect of the reductions on the research centers. In addition to requiring that the grantee develop a greater cost consciousness in administering grant funds, some planned activities will need to be delayed and certain purchases of supplies and equipment be curtailed. These reductions will somewhat slow our efforts in integrating basic research with applied research and transfer activities.

Mr. Early. To what extent will NIH's ability to conduct clinical trials to be affected?

Dr. Wyngaarden. Funding reductions in the FY 1986 and FY 1987 research centers program should not impact on NIH's support of clinical trials. Clinical trials are rarely supported through the research centers mechanism.

Mr. Early. It would seem to me that such substantial reductions would have a significant and adverse effect on your multi-disciplinary and clinical research programs, clinical trials, and the ability to introduce the new advances from basic and clinical research into the community at large. Doctor, are you and your Institute Directors concerned about this matter?

Dr. Wyngaarden. Admittedly, we are concerned about the reduction in the FY 1987 request of 11 research centers from the FY 1986 revised estimate. However, the research centers program sufficiently complements our basic research program by translating basic research discoveries into clinical research.

Mr. Early. Doctor, in your professional judgment, as a scientist, do you think this is a good or wise proposal?

Dr. Wyngaarden. The reduction in the research centers program in FY 1987 will, to some degree, decrease the pace at which basic research advancements are tested and transferred to clinical practice.

RESEARCH FACILITIES

Mr. Early. Last year, we discussed the failure of interagency plans to go forward with a comprehensive survey of academic research facilities due to OMB's withdrawal of its previous approval. At that time, you indicated that NIH was conducting pilot studies of a survey instrument, but that OMB had not cleared the survey on the basis that NIH had not demonstrated that available data were not adequate. What is the status of this project? Do you plan to go forward with the survey? If not, why not?

Dr. Wyngaarden. In February 1985, NIH reported to the Congress on its participation in an envisioned interagency effort to conduct a study of the Nation's research facilities. After the OMB first concurred in and then withdrew its approval for conduct of the interagency study in October 1984, NIH began to develop an independent approach to assessing biomedical research facilities needs. Since that time, the NIH has developed and tested survey forms designed to secure the kinds of information that would be needed to formulate responsibly the requested long-term plans. A plan for a full-scale survey has been developed in preparation for review within the Executive Branch under the terms of the Paperwork Reduction Act.

Late last year, the NIH elected to reassess its plans because of the National Science Foundation (NSF) authorization legislation passed in November 1985, which directs that agency to conduct the necessary surveys and to report to the Congress every 2 years on the research facilities needs of universities. The NIH has initiated discussions with the NSF to determine how the facilities needs specific to biomedical research might best be assessed within the transscience scope of the charge to NSF. The first NSF report is due September 1, 1986.

Mr. Early. Are you familiar with the study conducted by the White House Science Council Panel on the health of U.S. colleges and universities?

Dr. Wyngaarden. Yes. Several NIH staff offices have provided information upon request and followed the study's progress as indicated by preliminary reports such as that which appeared in Science on January 31, 1986.

Mr. Early. The panel has recommended that Federal reimbursement to universities for use or depreciation of facilities and equipment engaged in research should be based on "realistic useful lifetimes." Basically, the panel recommended that the lifetimes used in determining use charges associated with facilities and equipment be significantly reduced (50 yrs. to 20 yrs., and 15 yrs. to 5-10 yrs., respectively). Do you think changes are needed in this area? In general, would you agree with these recommendations?

Dr. Wyngaarden. There is evidence in support of the panel's recommendations for reduction in the "lifetimes" currently used for determining use charges. However, the "use allowance" approach to facilities/equipment funding represents only one permissible approach. The second--depreciation allowances--is not predicated on a pre-set lifetime, but *rather*, varies according to the type of building or equipment and other factors affecting the expected useful life of the assets. Universities are free to adopt the depreciation approach. An NIH-funded national survey of academic biomedical research equipment that was conducted in 1984 found that 60 percent of the equipment that was 6 to 10 years old was in less than excellent working condition. Correspondingly definitive national data about research facilities are not available. However, an NIH-funded pilot study of nine academic institutions in 1985 showed that, in the institutions studied, over 53 percent of facilities constructed in 1968 or earlier were in need of major repair or replacement. In contrast, 90 percent of the facilities constructed between 1968 and 1979 were judged in satisfactory condition. In any event, there remain over-arching policy questions of whether the Federal Government, through indirect cost payments, should assume a larger share of these costs than heretofore and whether such action is consistent with the contemporary interest within both the Congress and the Executive Branch in containing indirect cost expenditures.

Mr. Early. Provide for the record a series of tables showing by mechanism and by Institute, the additional amounts over the FY 1986 enacted appropriation, the FY 1986 post-sequestration level, and the FY 1987 budget request required to maintain in FY 1987 the program level of the FY 1986 enacted appropriation bill.

Dr. Wyngaarden. The tables on the following nine pages show the amounts needed in FY 1987 over the FY 1986 appropriation, the FY 1986 level after sequestration, and the FY 1986 revised level to support current services; that is, the cost in FY 1987 of providing for all commitments, for the same number of new and competing research project grants as in these FY 1986 levels, and for an inflation allowance in other mechanisms.

BUDGET INCREASE

Mr. Early. Doctor, if there were an increase over and above the total amount requested for NIH. How would you use this increase? What would your priorities be?

Dr. Wyngaarden. The NIH's highest priority is the support of investigator-initiated research funded through research project grant awards. If additional funds were provided, we would first increase support for this important mechanism. Funds would be added to support the direct costs of project grants at levels more consis-

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ADDITIONAL AMOUNTS NEEDED IN 1987 TO MAINTAIN
PROGRAM LEVELS OF 1986 APPROPRIATION
(In thousands)

	NCI		NHLBI		NIDR		NIDDKD		NINCDS	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:										
Noncompeting	68	$45,149	69	$48,543		$4,086		$33,952	43	$20,255
Admin. supp.		270		48	--	---			(10)	346
Competing	44	27,521	76	42,473	39	6,240	71	32,768	108	106,658
Subtot., C	44	27,521	76	42,473	39	6,240	71	32,768	108	26,532
Subtot.,RPG	112	72,940	145	91,064	39	10,326	71	66,720	151	47,133
Research Ctrs:										
Spec/comp.	1	6,676		14,617		2,115		7,741		4,282
GCRC										
Biotech										
LASPR										
Gorgas										
Subtotal	1	6,676		14,617		2,115		7,741		4,282
Other Res.:										
Careers		283		1,949		172	11	1,237	10	1,042
Organ sys.		241								
Clin. ed.	13	2,493								
Coop. cl.	13	2,058	1	723						84
BRS										
MBRS	43	139		336		6		105		17
Other	4	420	-1	512	10	176	1	122	2	259
Subtotal	73	5,634		3,520	10	354	12	1,464	12	1,402
Total,RGs	186	85,250	145	109,201	49	12,795	83	75,925	163	52,817
Training										
Indiv.	15	524	31	1,138	10	251	5	251	9	299
Instit.	78	2,969	179	6,947	-2	136	62	2,150	18	647
Total	93	3,493	210	8,085	8	387	67	2,401	27	946
Contracts	13	11,949		3,956	2	292	3	1,619	7	2,110
Intramural		13,401		7,403		18		4,463		3,411
RM&S		4,156		2,016		257		1,200		1,284
Control		5,166								
Construct.		3,331		3,435						
Total, IRDs		126,746		134,096		13,749		85,608		60,568

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ADDITIONAL AMOUNTS NEEDED IN 1987 TO MAINTAIN
PROGRAM LEVELS OF 1986 APPROPRIATION
(In thousands)

	NIAID		NIGMS		NICHD		NEI		NIEHS	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:										
Noncompeting	58	$32,995	152	$56,118	16	$19,738	14	$18,850		$3,089
Admin. supp.		76				860		(870)		36
Competing	91	21,526	283	45,761	27	12,377	108	19,706	6	2,324
Subtot., C	91	21,526	283	45,761	27	12,377	108	19,706	6	2,324
Subtot.,RPG	149	54,597	435	101,879	43	32,975	122	37,686	6	5,449
Research Ctrs:										
Spec/comp.	4	2,332	5	4,079		5,103		950		1,538
GCRC										
Biotech										
LASPR										
Gorgas										
Subtotal	4	2,332	5	4,079		5,103		950		1,538
Other Res.:										
Careers	3	170	-2	(41)	5	510	3	298	3	223
Organ sys.										
Clin. ed.										
Coop. cl.										
BRS										
MBRS		19				49		27		31
Other			19	480		81	15	374		41
Subtotal	3	189	17	439	5	640	18	699	3	295
Total,RGs	156	57,118	457	106,397	48	38,718	140	39,335	9	7,282
Training										
Indiv.	30	833	151	3,486	8	304	10	334	5	77
Instit.	86	1,936	291	5,590	32	1,067	8	335	30	680
Total	116	2,769	442	9,076	40	1,371	18	669	35	757
Contracts	13	3,661		52	-6	1,945	-7		10	4,630
Intramural		3,789		36		1,452		(2)		3,322
RM&S		1,002		545		772		142		347
Control										
Construct.								3,435		
Total, IRDs		68,339		116,106		44,258		43,579		16,338

DHHS - National Institutes of Health

ADDITIONAL AMOUNTS NEEDED IN 1987 TO MAINTAIN
PROGRAM LEVELS OF 1986 APPROPRIATION
(In thousands)

	NIA		NIAMSD		DRR		FIC		TOTAL	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:										
Noncompeting	21	$12,084		$10,028					441	$304,887
Admin. supp.		5	(-1)						(9)	771
Competing	56	12,710	51	10,624					960	260,562
Subtot., C	56	12,710	51	10,624					960	260,562
Subtot.,RPG	77	24,799	51	20,652					1401	566,220
Research Ctrs:										
Spec/comp.		1,010		1,953					10	52,396
GCRC					2	9,042			2	9,042
Biotech					1	3,195			1	3,195
LASPR						1,706				1,706
Gorgas								$66		66
Subtotal		1,010		1,953	3	13,943		$66	13	66,405
Other Res.:										
Careers	3	442	4	300		14			40	6,599
Organ sys.										241
Clin. ed.									13	2,493
Coop. cl.									14	2,865
BRS					566	66,537			566	66,537
MBRS		81		29		1,825			43	2,664
Other	4	295	1	99		876	7	255	62	3,990
Subtotal	7	818	5	428	566	69,252	7	255	738	85,389
Total,RGs	84	26,627	56	23,033	569	83,195	7	321	2152	718,014
Training										
Indiv.	5	101	2	77		3			281	7,678
Instit.	40	609	9	437	1	41			832	23,544
Total	45	710	11	514	39	1,119			1113	31,222
Contracts	6	1,706	1	429		371			42	32,720
Intramural		1,491		551						39,335
RM&S		71		(729)		570		227		11,860
Control										5,166
Construct.										10,201
Total, IRDs		30,605		23,798		84,180		548		848,518

National Library of Medicine	3,630
Office of the Director	13,523
Buildings and Facilities	4,908
Total, NIH	870,579

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ADDITIONAL AMOUNTS NEEDED IN 1987 TO MAINTAIN PROGRAM LEVELS OF 1986 APPROPRIATION AFTER SESQUESTRATION

(in thousands)

	NCI		NHLBI		NIDR		NIDDKD		NINCDS	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:										
Noncompeting	68	$33,549	69	$48,508		$4,086		$33,952	43	$11,261
Admin. supp.		-25		-4	--	---			(9)	302
Competing	44	19,823	76	42,473	39	6,240	71	32,768	108	102,072
Subtot., C	44	19,823	76	42,473	39	6,240	71	32,768	108	21,946
Subtot.,RPG	112	53,347	145	90,977	39	10,326	71	66,720	151	33,509
Research Ctrs:										
Spec/comp.		2,828		14,594		2,062		7,741		2,964
GCRC										
Biotech										
LASPR										
Gorgas										
Subtotal		2,828		14,594		2,062		7,741		2,964
Other Res.:										
Careers	-5	-26		923	-3	-16	4	724		487
Organ sys.	0	196								
Clin. ed.	13	2,282								
Coop. cl.	-11	-189	1	647						39
BRS										
MBRS	40	-13		223				49		8
Other	3	266	-1	102	7	120		58		238
Subtotal	40	2,516		1,895	4	104	4	831		772
Total,RGs	152	58,691	145	107,466	43	12,492	75	75,292	151	37,245
Training										
Indiv.	6	317	31	869	7	195	4	222		176
Instit.	32	1,795	179	5,417	-9	-12	25	1,256		340
Total	38	2,112	210	6,286	-2	183	29	1,478		516
Contracts	-1	5,253		1,165		82	2	761	4	1,523
Intramural		3,428		4,655		-834		2,114		1,166
RM&S		1,115		-273		-22		570		369
Control		2,306								
Construct.		3,242		3,287						
Total, IRDs		76,147		122,586		11,901		80,215		40,819

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ADDITIONAL AMOUNTS NEEDED IN 1987 TO MAINTAIN
PROGRAM LEVELS OF 1986 APPROPRIATION AFTER SESQUESTRATION
(In thousands)

	NIAID		NIGMS		NICHD		NEI		NIEHS	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:										
Noncompeting	58	$32,995	152	$56,118	16	$19,738	14	$18,850		$1,361
Admin. supp.		76				860		-870		12
Competing	91	21,526	283	45,761	27	12,377	108	19,706	6	1,566
Subtot., C	91	21,526	283	45,761	27	12,377	108	19,706	6	1,566
Subtot.,RPG	149	54,597	435	101,879	43	32,975	122	37,686	6	2,939
Research Ctrs:										
Spec/comp.	4	2,058	4	3,622		5,103		677		851
GCRC										
Biotech										
LASPR										
Gorgas										
Subtotal	4	2,058	4	3,622		5,103		677		851
Other Res.:										
Careers		-10	-3	-68		238	3	259	2	156
Organ sys.										
Clin. ed.										
Coop. cl.										
BRS										
MBRS		-2				49		12		15
Other		-40	15	134		81	15	321		1
Subtotal		-52	12	66		368	18	592	7	172
Total,RGs	153	56,603	451	105,567	43	38,446	140	38,955	8	3,962
Training										
Indiv.	14	381	118	2,726	4	189	10	218	3	37
Instit.	74	1,879	193	3,783	7	559	8	219	30	528
Total	88	2,260	311	6,509	11	748	18	437	33	565
Contracts	9	2,474		52	-9	908	-7			2,193
Intramural		959		36		-372		-6		954
RM&S		286		545		94				47
Control										
Construct.								3,287		
Total, IRDs		62,582		112,709		39,824		42,673		7,721

DHHS - National Institutes of Health

ADDITIONAL AMOUNTS NEEDED IN 1987 TO MAINTAIN
PROGRAM LEVELS OF 1986 APPROPRIATION AFTER SESQUESTRATION
(In thousands)

	NIA		NIAMSD		DRR		FIC		TOTAL	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:										
Noncompeting	21	$12,084		$10,028					441	$282,530
Admin. supp.		5	(-1)						(8)	356
Competing	56	12,710	51	10,624					960	247,520
Subtot., C	56	12,710	51	10,624					960	247,520
Subtot.,RPG	77	24,799	51	20,652					1401	530,406
Research Ctrs:										
Spec/comp.		545		1,953					8	44,998
GCRC					2	4,934			2	4,934
Biotech					1	1,600			1	1,600
LASPR						296				296
Gorgas								$57		57
Subtotal		545		1,953	3	6,830		$57	11	51,885
Other Res.:										
Careers	1	229		140		-1			-1	3,035
Organ sys.										196
Clin. ed.									13	2,282
Coop. cl.									-10	497
BRS					559	62,253			559	62,253
MBRS		65		14		708			40	1,128
Other	1	246		46		318		47	40	1,938
Subtotal	2	540		200	559	63,278		47	641	71,329
Total,RGs	79	25,884	51	22,805	562	70,108		104	2053	653,620
Training										
Indiv.	3	66		36					200	5,432
Instit.	17	311		205	-1	-4			555	16,276
Total	20	377		241	37	1,071			755	21,708
Contracts	4	1,091	1	88		138			3	15,728
Intramural		555		262						12,917
RM&S		35		-824		90		-164		1,868
Control										2,306
Construct.										9,816
Total, IRDs		27,942		22,572		70,332		-60		717,963

National Library of Medicine	767
Office of the Director	8,285
Buildings and Facilities	6,844
Total, NIH	733,859

DHHS - National Institutes of Health

ADDITIONAL AMOUNTS NEEDED IN 1987 TO MAINTAIN
PROGRAM LEVELS OF 1986 COLUMN OF 1987 PRESIDENT'S BUDGET
(In thousands)

	NCI		NHLBI		NIDR		NIDDKD		NINCDS	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:										
Noncompeting\		$26,831	4	$34,595		$4,086		$33,952		$2,537
Admin. supp.		-25		-4	--	---			(9)	302
Competing	-30	12,744	7	27,727	39	6,240	-2	20,434	60	92,380
Subtot., C	-30	12.744	7	27,727	39	6,240	-2	20,434	60	12.254
Subtot.,RPG	-30	39,550	11	62,318	39	10,326	-2	54,386	60	15,093
Research Ctrs:										
Spec/comp.		2,828		14,594		2,062		7,741		2,964
GCRC										
Biotech										
LASPR										
Gorgas										
Subtotal		2,828		14,594		2,062		7,741		2,964
Other Res.:										
Careers	-5	-26		924	-3	-16	4	724		487
Organ sys.		196								
Clin. ed.	13	2,282								
Coop. cl.	-11	-189	1	647						39
BRS										
MBRS	40	-13		223				49		8
Other	3	266	-1	102	7	120		58		238
Subtotal	40	2,516		1,896	4	104	4	831		772
Total,RGs	10	44,894	11	78,808	43	12,492	2	62,958	60	18,829
Training										
Indiv.	6	317	14	869	7	195	4	222		176
Instit.	32	1,795	113	5,417	-9	(12)	25	1,256		340
Total	38	2,112	127	6,286	-2	183	29	1,478		516
Contracts	-1	5,253		1,165		82	2	761	4	1,523
Intramural		3,428		4,655		-834		2,114		1,166
RM&S		1,115		-273		-22		570		369
Control		2,306								
Construct.		3,242		3,287						
Total, IRDs		62,350		93,928		11,901		67,881		22,403

DHHS - National Institutes of Health

ADDITIONAL AMOUNTS NEEDED IN 1987 TO MAINTAIN
PROGRAM LEVELS OF 1986 COLUMN OF 1987 PRESIDENT'S BUDGET
(In thousands)

	NIAID		NIGMS		NICHD		NEI		NIEHS	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:										
Noncompeting		$24,795	-1	$40,291		$16,507		$16,908		$1,361
Admin. supp.		76				860		-870		12
Competing	29	12,623	121	25,233	11	9,754	81	16,692	6	1,566
Subtot., C	29	12,623	121	25,233	11	9,754	81	16,692	6	1,566
Subtot.,RPG	29	37,494	120	65,524	11	27,121	81	32,730	6	2,939
Research Ctrs:										
Spec/comp.	4	2,058	4	3,622		5,103		677		851
GCRC										
Biotech										
LASPR										
Gorgas										
Subtotal	4	2,058	4	3,622		5,103		677		851
Other Res.:										
Careers		-10	-3	-68		238	3	259	2	156
Organ sys.										
Clin. ed.										
Coop. cl.										
BPS										
MBRS		-2				49		12		15
Other		-40	15	134		81	15	321		1
Subtotal		-52	12	66		368	18	592	2	172
Total,RGs	33	39,500	136	69,212	11	32,592	99	33,999	8	3,962
Training										
Indiv.	14	381	118	2,726	4	189	10	218	3	37
Instit.	74	1,879	193	3,783	7	559	8	219	30	528
Total	88	2,260	311	6,509	11	748	18	437	33	565
Contracts	9	2,474		52	-9	908	-7			2,193
Intramural		959		36		-372		-6		954
RM&S		286		545		94				47
Control										
Construct.								3,287		
Total, IRDs		45,479		76,354		33,970		37,717		7,721

DHHS - National Institutes of Health

ADDITIONAL AMOUNTS NEEDED IN 1987 TO MAINTAIN PROGRAM LEVELS OF 1986 COLUMN OF 1987 PRESIDENT'S BUDGET

(In thousands)

	NIA		NIAMSD		DRR		FIC		TOTAL	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:										
Noncompeting		$7,913		$10,028					3	$219,804
Admin. supp.		5	(-1)						(8)	356
Competing	32	8,135	25	6,511					379	159,913
Subtot., C	32	8,135	25	6,511					379	159,913
Subtot.,RPG	32	16,053	25	16,539					382	380,073
Research Ctrs:										
Spec/comp.		545		1,953					8	44,998
GCRC					2	4,934			2	4,934
Biotech					1	1,600			1	1,600
LASPR						296				296
Gorgas								$57		57
Subtotal		545		1,953	3	6,830		$57	11	51,885
Other Res.:										
Careers	1	229		140		-1			-1	3,036
Organ sys.										196
Clin. ed.									13	2,282
Coop. cl.									-10	497
BRS					559	62,253			559	62,253
MBRS		65		14		708			40	1,128
Other	1	246		46		318		47	40	1,938
Subtotal	2	540		200	559	63,278		47	641	71,330
Total,RGs	34	17,138	25	18,692	562	70,108		104	1034	503,288
Training										
Indiv.	3	66		36					183	5,432
Instit.	17	311		205	-1	-4			489	16,276
Total	20	377		241	37	1,071			672	21,708
Contracts	4	1,091	1	88		138			3	15,728
Intramural		555		262						12,917
RM&S		35		-824		90		-164		1,868
Control										2,306
Construct.										9,816
Total, IRDs		19,196		18,459		70,332		-60		567,631

National Library of Medicine	767
Office of the Director	-15,715
Buildings and Facilities	6,844
Total, NIH	559,527

tent with study section recommendations and committed amounts. In addition, NIH would support a greater number of competing awards. Many experts in biomedical research believe that the optimal award rate for research project grants is about 45 percent of approved applications. At this award rate, a significant portion of potentially valuable science would receive support, enabling us to pursue many research opportunities now before us.

We would also increase support for the research training program. Ideally, we would like to fund about 10,500 full-time training positions, the number recommended by the National Academy of Sciences. In addition, we would like to provide inflation allowances in stipends, tuition, and related costs.

NIH would provide support for about 536 research centers, the same number as would receive funding under the FY 1986 appropriation level. In addition, NIH would provide average cost increases to enable center projects to keep pace with inflation.

Other extramural mechanisms, such as other research grants and R&D contracts, and the NIH in-house activities, such as intramural research, would receive funding at the current services level. Clinical trials is another area which would receive emphasis.

NEW INITIATIVES

Mr. Early. Doctor, when I think of science and research, I think of progress and advancement. When I see this Administration's budget requests, I see retreat--from further improving the health and quality of life for our citizens--and a slipping away of our competitive edge in the life sciences.

Will NIH be able to undertake any new initiatives under the FY 1987 budget request? With a budget request like this, are you as likely to take a chance on something brand new?

Dr. Wyngaarden. Within the FY 1987 budget, we will be able to undertake some new initiatives, primarily through the support of 5,100 new and competing research project grants. We will also be able to support a few new clinical trials.

Mr. Early. Doctor, when you have to retreat--when you can't take advantage of the new opportunities when they present themselves; when you can't vigorously pursue initiatives, how long does it take to make up "lost ground"? Do you ever really make up that lost ground?

Dr. Wyngaarden. Although none of us is actually able to make up for lost time, I believe that research opportunities are never totally lost. The investigative mind continues to function, to search for answers, to develop new ways of tackling scientific problems--regardless of the immediate availability of research support. Eventually, the truly excellent projects will be funded.

BUDGET REQUEST

Mr. Early. Doctor, would you want to see this type of budget request for NIH for the next few years? Why not?

Dr. Wyngaarden. Ideally, of course, I would like to see greater funding for the NIH. There are many opportunities to be pursued. However, I recognize that, at a time when all Government activities are required to make downward adjustments in spending to achieve deficit reduction targets, the NIH must share in those considerations.

Mr. Early. Do you think the research conducted and supported by NIH is at least important as that of the Defense Department? Why?

Dr. Wyngaarden. As Director of the NIH and as a biomedical researcher, I am, of course, biased in my opinion of the value of the research supported and conducted by the NIH. This research has had a profound and beneficial influence on the modern practice of medicine and on the state of the health of people throughout the Nation. As far as the relative merits of the research supported and conducted by the Defense Department, I believe this issue is best left to the determination of the Administration and Congress in their development of the budgets for the various agencies.

NURSING CENTER

Mr. O'Brien. The FY 1985 supplemental appropriations bill appropriated $5 million for the purpose of a National Center for Nursing Research. Please explain where that money is right now and when you can expect to start using it for the Center, assuming that the rescission request is not approved?

Dr. Wyngaarden. The funding is being held by the OMB pending resolution of the FY 1986 rescission proposal and the availability of an FY 1987 budget for the Center. If the rescission is not approved by the Congress, the funds will be used upon their release from OMB.

Mr. O'Brien. In the creation of the National Center for Nursing Research at the NIH, the legislative intent was also to transfer the nursing research, nursing research traineeship funds, and the FTEs from the Division of Nursing to the NIH. When can we expect that to happen? How many FTEs will be transferred to the new National Center?

Dr. Wyngaarden. The National Center for Nursing Research (NCNR) cannot be established at NIH until congressional action has been taken on the President's rescission proposal. If Congress restores the funds for these programs, the Center can be established and the transfer can take place.

We understand that the Health Resources and Services Administration is prepared to transfer 8 FTEs to the NCNR at the NIH.

Mr. O'Brien. Have you established a space for the Nursing Research Center? When do you expect the Center to be operational?

Dr. Wyngaarden. Interim space to house the Center has been identified in the Lister Hill Building on the NIH campus; the Center's ultimate location is planned to be in Building 31. If the rescission proposal is not approved by Congress, the NIH will complete action on the establishment of the Center and operations can then proceed.

Mr. O'Brien. Please explain the process for selecting a Director of the Center. When do you expect to have a Director appointed?

Dr. Wyngaarden. As soon as permission is received from the Secretary, DHHS, to establish an SES position for the NCNR Director, the NIH will appoint a search and screen committee. It normally takes from 6 to 9 months of committee activity before an appointment can be made.

ALZHEIMER DISEASE CENTERS

Mr. O'Brien. Please give me the status of the Alzheimer Disease Centers. How ~~many in~~ existence, and where? How many are projected for FY 1986, FY 1987, and where will they be?

Dr. Wyngaarden. The National Institute on Aging now supports 10 Alzheimer Disease Research Centers, located in the following universities and medical schools:

- Duke University
- University of California at San Diego
- University of Pittsburg
- Harvard University
- University of Washington
- Mt. Sinai School of Medicine
- University of Southern California, Los Angeles
- University of Kentucky
- The Johns Hopkins University
- Washington University

These centers will continue through FYs 1986 and 1987. No additional centers are planned at this time.

Mr. O'Brien. If you read this morning's Washington Post, you know of the growing, mainly silent, crushing fear in the population about contracting Alzheimer disease. At this point, I am not concerned about the cost problem--that is the subject for Dr. Bowen.

However, I am deeply concerned about the appearance we may be giving in this budget that Alzheimer research questions have been pushed down the research priority scale for the NIH.

What can we tell our older population, and the middle age population, about what is being done at NIH regarding this dreaded disease?

Dr. Wyngaarden. In FY 1985, the NIH spent slightly more than $43.9 million for research on the causes, diagnosis, and treatment of Alzheimer disease.

The theories of what causes Alzheimer disease have matured in a rich atmosphere of research on the neuroscience of aging. The basic theories have not changed. We still think that genetics, environmental factors, immunologic changes, and perhaps the introduction of a slow virus may all play a role in the development of Alzheimer disease. Nonetheless, we are looking for more basic answers. Scientists are examining the fundamental processes that underlie neurotransmitter changes and other such phenomena. As a result, we are beginning to see how the leading theories converge and coalesce.

Since the late 1960's, some scientists have speculated that Alzheimer disease might result from a so-called "slow virus" infection, caused by an infectious agent that hides within the body for years before producing devastating disease. Previous studies have identified the infectious "prion" protein associated with some slow-virus disorders. More recently it has been demonstrated that the prion is part of a larger protein present in both normal and infected cells. In normal cells, the larger protein is completely broken down by enzymes; in infected cells, the defective breakdown leaves the prion intact. This prion has a fibrous structure that resembles certain filaments found in the brains of Alzheimer patients upon autopsy.

There is no single medical test that can diagnose Alzheimer disease. The early symptoms of Alzheimer disease--forgetfulness, confusion, changes in mood and behavior--are also symptoms of a large number of other diseases. As a result, physicians who suspect Alzheimer disease use a battery of tests, including medical history, clinical examination, blood and other laboratory tests, psychological tests, and radiologic scans. The diagnosis of Alzheimer disease is made only after all other possibilities have been excluded.

Nonetheless, we are better able to diagnose Alzheimer disease today than ever before. Several successive generations of psychological tests have begun to focus more closely on the early and progressive signs of Alzheimer disease. New diagnostic tools such as nuclear magnetic resonance imaging can look closer and deeper into the working human brain.

Several times during the past year, the media have publicized major improvements in Alzheimer patients given experimental drugs. Each time, a closer examination revealed that there is still work to be done. One pressing need is for a test that can show the potential of any new drug. Scientists are using a variety of tests to evaluate their patients' response to new drugs, without knowing how objective the results are.

At the Bronx Veterans Administration Medical Center in New York, an NIA grantee has devised a simple test that focuses on the major symptoms of Alzheimer disease and can be used to evaluate patients in all stages of the disease. The test is brief, easy to administer, and can be used anywhere the patient is. It looks at such things as memory, language, mood, and behavior, and it rates the majority of the items on a five-point scale of severity so that subtle changes can be detected. It is hoped that the Alzheimer Disease Assessment Scale will be sensitive enough to measure the success of any future attempts to treat Alzheimer disease.

The NIA supports major research activities on Alzheimer disease and related dementias in older people, including 10 Alzheimer Disease Research Centers. These centers have begun to produce important scientific knowledge. At one of the centers, it has been found that nuclear magnetic resonance imaging can detect very early signs of small strokes or multi-infarct dementia and distinguish them from Alzheimer disease. This will enable physicians to institute appropriate treatments, thus preventing further deterioration. Research at other centers is defining the genetic component of Alzheimer disease.

One of the charactertistics of Alzheimer disease is the presence of amyloid fiber deposits in the brain's blood vessels. An NIA-supported scientist has isolated and analyzed these amyloid fibers of Alzheimer patients and found a unique protein not seen in healthy individuals. This work reveals yet another clue that Alzheimer disease is a systemic disorder, and may lead to a simple diagnostic test for the disease in the future.

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) conducts and supports research to understand the progressive, irreversible brain deterioration associated with Alzheimer disease. Areas of intense research interest are changes in brain chemistry, cell death from viral infections or environmental toxins, and genetic susceptibility to the disease. A disruption in one of the brain's chemical messenger systems, the cholinergic system, has been implicated in Alzheimer disease. An NIA/NINCDS grantee at The Johns Hopkins University has shown that one message pathway in the cholinergic system that deteriorates in the brains of Alzheimer victims is also destroyed in the rat model. This discovery might help explain why the brain's cortex and hippocampus, which lie at the end of this pathway, accumulate nerve fiber tangles and plaques characteristic of Alzheimer disease; and why Alzheimer patients lose shortterm memory governed by the cholinergic system but retain the longterm memory maintained by other chemical messenger systems.

A team of American and Italian investigators, completing a 3-year collaborative effort of the Italian National Research Council and the NINCDS, reported this year on the largest case-control study of Alzheimer risk factors. The findings revealed that people whose brothers or sisters have any form of dementia may be 11 times more likely than others to develop Alzheimer disease. The study also provided some support for earlier observations that severe head trauma may be a risk factor for Alzheimer disease, and that babies born to mothers over age 40 may be at greater risk for dementia later in life.

Other NIH research to understand the causes and mechanisms of Alzheimer disease includes efforts by scientists at the National Institute of Allergy and Infectious Diseases to identify animal diseases with similar characteristics, such as scrapie. Research at the Mount Sinai General Clinical Research Center--supported by the Division of Research Resources--has focused on the effect of drugs such as physostigmine in temporarily improving the memory of Alzheimer patients.

SUPERCOMPUTER

Mr. O'Brien. Last year, I questioned Dr. De Vita on the subject of a "super computer" and its potential for assisting in biomedical research. Please give me an update on planning for the acquisition of new computing power at the NIH.

Dr. Wyngaarden. On September 10, 1985, the National Cancer Institute signed a contract with Falcon Systems, Incorporated, a small business, for the acquisition and maintenance of a supercomputer system. The system is located at the Frederick Cancer Research Facility and on the NIH campus within the Laboratory of Mathematical Biology, Division of Cancer Biology and Diagnosis. This is the first and only supercomputer anywhere to be dedicated solely to biomedical research. A high-speed telecommunications network will link researchers on the NIH Bethesda campus to the supercomputer. In addition, the telecommunications network will tie into the DHHS telecommunications center, which will allow other Department users to access the system. While use of the supercomputer will begin with NCI research, soon the facility will be scaled up to support not only the NIH and DHHS users on a cost recovery basis, but also extramural scientists through grants-in-kind. The dedicated system gives scientists direct control over the supercomputer operation and application, so that the computer serves the scientists, rather than the other way around.

Mr. O'Brien. Last year the estimate ranged from $10 million to $40 million for such a machine. What is the cost estimate now for obtaining a supercomputer for NIH?

Dr. Wyngaarden. As mentioned above, the contract for the acquisition of the supercomputer system was signed on September 10, 1985. The contract was for $11,104,806. This amount includes not only the Cray Research central processing unit (X-MP/22U) but also the two front-end computers (VAX 11-785 and 8600) as well as supporting software, annual maintenance cost, and one-time installation and training costs.

Mr. O'Brien. Please provide for the record a fairly detailed statement of why a super computer would be of benefit to NIH. How does NIH now obtain machine time--on a supercomputer--when research dictates the need? Is there a specific office or department in NIH that makes decisions about the contracting for or renting time of a super computer?

Dr. Wyngaarden. Over the past decade we have witnessed the advent of a "biological revolution" manifested by an explosion of technology including recombinant DNA technology, gene cloning, rapid DNA sequencing, and the application of monoclonal antibodies in the detection and treatment of disease. This has led to a complex of data that, like the study of DNA previously, would seem to be impossible to fully analyze. With the rapid increase in computer technology, however, the use of supercomputers in biology brings the solution to these extremely complex problems into the realm of reality.

It is not possible for anyone to anticipate of all the applications a supercomputer will have. However, the supercomputer will provide a milieu for the creative intellect to expand. At the present time, we can identify a number of urgent scientific problems that need the power of a supercomputer.

Sequence Analysis

Libraries of genes mapped on their chromosomes are growing at more than three genes per week. The entire human gene complement consists of some 10,000 active genes. Nucleic acid sequences of the genes are being collected in a national data repository at a rate of more than 100,000 bases per month. The database currently contains sequence information on almost 5.0 million bases. To store data on all human, animal, plant, and viral gene sequences calls for a vast data storage capacity.

The supercomputer will be able to examine the estimated tens of thousands of base proteins that are sequenced each month at NIH alone. Moreover, with the new capability, these can be analyzed and compared in full detail without the need to wait for data publication.

To understand the complex interaction of large molecules in normal and abnormal cells, scientists must know the nucleic acid sequences of genes, the structure of their protein products, and how the proteins affect the cell. Because protein structures are frequently deduced from sequences of nucleic acids, the data can be derived from spliced genes, overlapping genes, or genes on either of the two DNA strands. This means that the search must be done for all possible translations, leading to some 200,000 amino acid residues to search each month. Detecting protein relationships is even more complex.

Predicting RNA secondary structures from DNA sequence data is important for understanding how the mRNA is processed and expressed. Currently, it takes two and a half hours to sequence 1,000 DNA bases and 24 hours for 2,000 bases. With hundreds of these analyses being done each month, the supercomputer can make the information rapidly available for scientists to understand how mRNA functions as an intermediary between the DNA and protein.

Crystallography

The value of x-ray crystallography in understanding proteins is growing rapidly. Scientists use crystallography to determine the atomic structure of a substance in crystalline form. The atoms of a molecule diffract x-rays to produce shadows. From these diffraction patterns, scientists can calculate the three-dimensional atomic structure of the molecule.

Crystallographers are now working on the creation of two materials that will clarify the molecular events that occur when a cell becomes cancerous: 1) a protein synthetically derived from constituent amino acids; and 2) an altered protein produced by modifying the sequences of an existing protein. With these capabilities, understanding of protein structure and function will expand enormously.

The supercomputer provides the speed for the multiple calculations to determine the elements of the three-dimensional structure and, with its graphics capabilities, the flexibility to manipulate the coordinates of these elements to find the correct fit.

Molecular Dynamics

Although a crystal structure gives a static representation of a molecule, it does not show how different parts of a protein move to interact with other substrates and regulatory molecules. One way to examine these properties is with molecular dynamic calculations. By manipulating the computer-imaged molecule, scientists can show how all atoms are moved step by step, according to changes in time and physics. The movie-like action can show the opening and closing of sites as well as the flexing and contracting of protein chains.

Thousands of computations are needed to generate computerized images of the steps representing the transitions from one molecular state to another. Scientists use similar methods to predict how drug molecules interact with proteins and how a modified protein sequence differs from its parent. These molecular dynamics images have changed how scientists perceive proteins.

Three-dimensional Graphic Analysis

With methods similar to those molecular dynamics, scientists can display drawings of proteins in three dimensions on a computer. For maximal use of this method to help design drugs and proteins, scientists need very fast computation and data transfer. The supercomputer can compute and transfer data more than 100 times faster than small computers.

Image Analysis

Speeds not obtainable on ordinary computers are needed for fast analyses of large digital images obtained from radioautographs (images obtained with radioactive markers on photographic film), light microscopes, and electron microscopes. The supercomputer can provide this speed.

Rapid Analysis of Databases

Large databases of patient information, clinical observations, mutations, sequences, and two- and three-dimensional images will require larger storage and faster retrieval capabilities. A supercomputer has, in addition to its fast central processor, a number of special processors that transfer data rapidly from storage discs to the computer's internal memory.

All these problems depend on applied and theoretical developments in numerical analysis, algorithms, geometry, statistics, and other areas of math acquiring powerful, general purpose computing. These tools are proving to be central to progress in the pursuit of solutions to cancer research problems. Oncogenes, and the subtle relationships with their non-oncogenic counterparts, are at the center of molecular cancer research. They are best defined and related to other functional genes through computerized sequence analysis. Their predicted proteins are classified by computers at a rate that would be nearly impossible through test tube methods. Quantum chemistry calculations are being used to understand the properties of both carcinogens and anticancer drugs, and their interaction with DNA and proteins. Protein engineering to make altered oncogenes, enzymes, antigens, and antibodies will need powerful computation to allow molecules to be simulated on the screen of a workstation in sufficient detail in order to predict their properties before they are made by costly laboratory methods. Powerful, general purpose computers are of great value in discovering the principles of special techniques such as imaging or electronic circuit design and in simulating their behavior prior to development of special purpose hardware. All these tools will be of use in developing diagnostic methods, understanding the biology, improving treatment, defining the etiology, and expanding prevention of cancer and other diseases.

Prior to NCI's acquisition of the supercomputer, supercomputer time was not realistically available to the biomedical research community. At the Advisory Meeting on Advanced Computers held in April 1984, leading scientists concerned with computer applications from the National Laboratories, other government agencies, and leading academic institutions unanimously recognized the urgent need for this kind of computing power. At that time, access to supercomputer time was not realistically available due to the high cost and the demand for time from those in the physical sciences.

The NCI, through its Division of Cancer Biology and Diagnosis, has established a review committee that will have as its responsibility the review of research proposals to use the supercomputer facility, and to set priorities relative to allocation of computer time.

NATIONAL CENTER FOR NURSING RESEARCH

Mr. Purcell. The FY 1987 budget proposed by President Reagan would eliminate funding for the newly enacted National Center for Nursing Research. Congress made its support of the new Center very clear in its override vote last fall. In light of that vote, what are your plans for establishing the National Center for Nursing Research in the context of the President's budget request?

Dr. Wyngaarden. Thus far, the NIH has undertaken various activities, including a review of the current nursing research and research programs supported by the Division of Nursing of the Health Resources and Services Administration. A study of the staff, budget, and space allocated to that operation has been made, and preliminary drafts of documents necessary to charter the Center's National Advisory Council have been prepared.

The President has asked for rescission of the $5 million currently appropriated for the initiation of the Center and of the $8.971 million in ongoing nursing research and research training programs to be transferred to NIH as the nucleus of the Center's activity. Pending action on this request, no further action can be taken to establish the Center at NIH.

Mr. Pursell. What is the timetable for establishing the new National Center for Nursing Research?

Dr. Wyngaarden. NIH cannot establish the National Center for Nursing Research (NCNR) unless the rescission proposal is disapproved.

Mr. Pursell. Specifically, when do you expect to have a National Center for Nursing Research Director on board?

Dr. Wyngaarden. As soon as permission is received from the Secretary, DHHS, to establish an SES position for the NCNR Director, the NIH will convene a search and screen committee. It normally takes from 6 to 9 months of committee activity before an appointment can be made.

Mr. Pursell. When do you expect the full-time-equivalent transfer from the Health Resources and Services Administration to the National Institutes of Health to take place?

Dr. Wyngaarden. The positions cannot be transferred pending Congressional resolution on the rescission proposal. If the proposal is disapproved, the transfer will take place as soon as practicable.

Mr. Pursell. When will the first National Center for Nursing Research grants review cycle at the NIH take place?

Dr. Wyngaarden. Applications submitted for the February 1, 1986, receipt date will be reviewed under the auspices of NIH.

Mr. Pursell. How can Federal support for nursing research be eliminated when it has been shown to save taxpayers' dollars in the long run? For example, nursing research on the care of premature infants resulted in treatment that reduced their length of hospital stay by an average of 4 days. The average cost of neonatal intensive care is estimated to exceed $13,000 and almost 7 percent of newborns in the United States are at risk because of low birth weight.

Dr. Wyngaarden. Elimination of a line item for support of nursing should not be viewed as an assessment by the Department that studies supported previously were ineffective. Studies like the one you describe should continue to compete successfully for research support from NIH, ADAMHA, or NCHSR.

Mr. Pursell. Where are you in establishing the National Center for Nursing Research and what monies have you requested for the Center?

Dr. Wyngaarden. As stated earlier, the Center cannot be established at NIH until congressional action has been taken on the President's rescission proposal. No funding for the Center has been requested in the FY 1987 budget.

Mr. Pursell. A 1983 Institute of Medicine report expressed strong reservations about the under-funding of nursing research. In addition, a recent study of nursing research prepared for the Office of Health Planning and Evaluation, Office of the Assistant Secretary for Health, United States Public Health Service, commented on the negative impact of erratic funding for nursing research. In light of these conclusions, shouldn't the Administration be asking for increased funding for nursing research rather than proposing its elimination?

Dr. Wyngaarden. The Administration has had to make difficult choices in its attempt to reduce the national deficit. Elimination of the nursing research program is only one of many such difficult decisions.

Mr. Pursell. A National Center for Nursing Research was established by Congress in November 1985 through the National Institutes of Health reauthorization bill. The President's veto of the measure was overridden by votes of 380 to 32 in the House and 89 to 7 in the Senate. Doesn't this overwhelming vote clearly reiterate the support of Congress to continue to fund nursing research at the Federal level?

Dr. Wyngaarden. The Congress made its support of the new Center very clear in its override vote last year. In the face of serious Federal deficits, however, some difficult decisions had to be made by the Administration in the development of the FY 1987 budget. The funding of nursing research at the Federal level was not considered to be of sufficiently high priority to merit support at this time of fiscal restraint.

OMB DISTRIBUTION OF FUNDS

Mr. Porter. Dr. Wyngaarden, prior to 1985, once Congress appropriated funds to carry out NIH programs, what was the process by which the Office of Management and Budget (OMB) distributed the funds?

Dr. Wyngaarden. After funds were appropriated by the Congress in the fiscal years prior to 1985, the NIH submitted individual requests for apportionment for each NIH appropriation for the total dollar amount by quarter, which were then reviewed and acted upon by OMB.

Mr. Porter. Did this process change for FY 1986?

Dr. Wyngaarden. In FY 1986, NIH was required to submit a single apportionment request for all NIH appropriations. The apportionment was split by quarter and by funding mechanism. Numbers of project grants and research centers were also identified. This procedure was initiated in FY 1985 after the Congress required NIH to fund a minimum number of new and competing grants and research centers and authorized $11 million in carryover funding for NIH as a whole. Based on these directives, OMB considered it necessary to modify the apportionment process.

Mr. Porter. What process is being used to implement the FY 1986 Gramm-Rudman cuts? Do the individual Institutes have the flexibility to set their own priorities, or are the cuts being applied uniformly across all line-items?

Dr. Wyngaarden. The documents to sequester funds under the provisions of the sequestration have been forwarded to the Congress through OMB. In applying the Balanced Budget and Emergency Deficit Control Act to NIH, the 4.3 percent reduction in funding was applied against the total amount appropriated to each NIH Institute as well as against each research mechanism and each program, project or activity, as identified in the conference report accompanying the 1986 appropriation. Although the 4.3 percent sequestration has been applied evenly across all mechanisms, the NIH has the authority and flexibility to reallocate funds within existing reprogramming rules, so long as they do not deviate from the few programs, projects and activities formally reported to the Congress under the sequestration procedures and so long as NIH meets the Congressional mandate to fund no fewer than 6,100 research project grants.

DISBURSEMENT DIRECTIVES

Mr. Porter. In addition to OMB instructions about the number of awards within selected categories, approximately how many other new directives are there regarding the way in which NIH can dispense the FY 1986 appropriated funds?

Dr. Wyngaarden. The primary directives are the Congressional mandate to fund 6,100 new and competing grants and the sequester of 4.3 percent. Under the current apportionment, the number and amount available for both competing and noncompeting research project grants and research centers are specified and there is no allowable variance from these numbers and amounts without OMB approval. To date, OMB has approved in an expedited fashion, all request for variance. All other mechanisms of support are detailed by amounts, except for research training (which also specifies number of training positions). For these other mechanisms (except Construction and Buildings and Facilities, for which there is no flexibility) the NIH may vary up to 3 percent from the apportionment plan. In addition, future year commitments are also detailed.

Mr. Porter. What process is required if the scientific leadership of NIH proposes to adjust certain funding distributions (i.e., to fund more comprehensive research centers and decrease funding for some grants)?

Dr. Wyngaarden. The process that would be required is dependent on the type of adjustment. Should NIH want to reduce the number of grants in order to support more centers, then the Congress would have to amend the FY 1986 Appropriations Act which specifies the number of project grants. Revised language has been proposed by the Administration. Should NIH propose to shift funds without changing the number of grants, through increased downward negotiations, then NIH would need to submit a revised apportionment plan to OMB for approval.

Mr. Porter. It would seem that this new process decreases the amount of flexibility for the Institute Directors, and requires them to devote more time to bureaucratic negotiation with OMB. It seems to me that this would have an adverse impact on promising new medical advances. Could you comment on this?

Dr. Wyngaarden. The additional constraints placed on NIH have introduced a new level of complexity into our financial and program planning. BID Directors, who formerly were able to initiate minor changes in mechanisms of support within their Institutes, must now have these changes reviewed in relationship to all of NIH and in some cases are required to obtain OMB and/or Congressional concurrence.

EDUCATIONAL BACKGROUNDS IN BIOMEDICAL SCIENCES

Mr. Porter. How many people with substantial education in the biomedical sciences (e.g., either a Ph.D. or M.D. or both) are employed by NIH? Prior to 1985, how many of these individuals were biomedical research and treatment program managers and/or involved in decision-making about research priorities?

Dr. Wyngaarden. The NIH currently employs 1,970 people with advanced degrees in the biomedical sciences; of these, 934 were biomedical research and treatment program managers prior to 1985 or were involved in decision-making regarding research priorities.

Mr. Porter. In contrast, do you know how many people with advanced education in the biomedical sciences are employed by OMB and are directly involved in assessing priorities regarding promising new leads in biomedical and treatment research?

Dr. Wyngaarden. Although OMB undoubtedly has a number of staff with advanced degrees in biomedicine, I do not know the number. Our discussions with OMB primarily deal with resource levels, management, and public policy.

MONDAY, MARCH 17, 1986.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

WITNESSES

DR. RUTH L. KIRSCHSTEIN, DIRECTOR

DR. JAMES B. WYNGAARDEN, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. LEO H. VON EULER, DEPUTY DIRECTOR, NIGMS

DR. ELKE JORDAN, ASSOCIATE DIRECTOR FOR PROGRAM ACTIVITIES, NIGMS

WILLIAM T. FITZSIMMONS, EXECUTIVE OFFICER, NIGMS

NANCY VESS, DEPUTY BUDGET OFFICER, NIGMS

DENNIS P. WILLIAMS, ACTING DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. NATCHER. At this time, we take up the budget request for the National Institute of General Medical Sciences, and we have before the committee Dr. Ruth L. Kirschstein, the Director.

Dr. Kirschstein, it is a pleasure to have you back before the committee. Before you give us your statement, if you would please, tell us who you have with you at the table there.

Dr. KIRSCHSTEIN. Thank you, Mr. Natcher.

To my right is Mr. Dennis Williams from the Department of Health and Human Services; Dr. James Wyngaarden, the Director of NIH; and Dr. Leo von Euler, the Deputy Director of the NIGMS; and to my left, the NIGMS Executive Officer, Mr. William Fitzsimmons; and next to him, Ms. Nancy Vess, the NIGMS Deputy Budget Officer; and Dr. Elke Jordan, the Institute's Associate Director for Program Activities.

Mr. NATCHER. We are delighted to have all of you before the committee again, and you may proceed.

OPENING STATEMENT

Dr. KIRSCHSTEIN. Mr. Chairman, I am pleased to be here again. I shall submit my statement for the record, but I would just like to emphasize certain points.

The programs of the National Institute of General Medical Sciences support basic untargeted biomedical research endeavors which continue to provide the knowledge through which specific diseases can be conquered.

The time it takes to develop basic concepts and to translate the knowledge so generated into leads regarding those many diseases not yet understood has been telescoped from years to often only months.

The fundamental biomedical research and research training efforts supported by the National Institute of General Medical Sciences are truly an investment in the future.

Mr. Chairman, I am delighted to be able to report, as did The New York Times yesterday, that two NIGMS grantees were among the 26 scientists awarded the National Science Medal by the President last Wednesday. They are Drs. Joan Steitz and George Palade of Yale University. Dr. Palade is a long-time friend of the members of this committee.

Nowhere is this natural flow of research endeavors from fundamental undifferentiated studies to disease-targeted activities better illustrated than by an account of the work of Drs. Michael Brown and Joseph Goldstein, this year's winners of both the Nobel Prize in Physiology or Medicine and the Lasker Award for basic medical research.

Their fundamental studies of steroids and lipoproteins as building blocks for cell membranes were supported by the NIGMS for a number of years. Gradually, these collaborative studies focused on a particular steroid chemical, cholesterol, and they discovered a mechanism that controls its metabolism inside the cell.

Since such basic studies of cholesterol are critical to an understanding of, and the development of preventive and treatment regimens for, atherosclerosis and other cardiovascular diseases, their research, originally supported by NIGMS, has been supported by the National Heart, Lung, and Blood Institute in recent years.

Over the past week, my colleagues have all told you about the research accomplishments occurring in their programs. For example, late last week Dr. Fauci gave you the latest information about AIDS.

The basic studies supported by NIGMS in years past in its genetics and cellular and molecular biology programs have provided fundamental knowledge regarding viral nucleic acids and how they replicate, about how molecules or viruses attach to the cell surface membranes and enter a cell, and about how a virus uses the cell's machinery to reproduce itself while destroying the cell, in the case of AIDS, destroying the T lymphocyte, one of the cells responsible for immune responses.

This research supported by NIGMS has permitted scientists studying AIDS to come to an understanding of the disease, as Dr. Fauci told you, and to know so much about the AIDS virus.

Recombinant DNA technology is enabling the development of the vaccines for AIDS. Furthermore, the fundamental studies supported by NIGMS related to the mechanism of action of drugs have greatly speeded the development of specific drugs for this dread disease.

Now, NIGMS is supporting work on new advances, the development of new, sophisticated research technologies, such as the rapid determination of DNA sequences, the isolation of very large DNA fragments, two-dimensional NMR, and more sophisticated X-ray crystallography.

There has been a dramatic expansion of the use of all these tools, as well as scientific disciplines such as chemistry. A recent National Academy of Sciences report says that chemistry will be the most important contributor to the solution of contemporary biomedical problems over the next 10 years. NIGMS provides the major support for research in chemistry at NIH.

All of these research advances, about which you have heard over the past week, have as their origins the untargeted, creative ideas of highly skilled, highly trained basic scientists.

The NIGMS, we are proud to say, has had a very large role in preparing such scientists through its research training programs. These programs have contributed about one-half of their graduates to the pool of researchers now supported by the categorical Institutes of NIH, researchers who are responsible for the advances my colleagues have outlined for you.

Thus, the programs of the NIGMS are aimed at providing the research manpower to keep up the momentum and at advancing knowledge of the fundamental cellular, molecular, chemical, pharmacologic and genetic processes so essential to developing better ways to understand, prevent and treat disease. But we must remember that there is so much yet to learn.

Mr. Chairman, the 1987 budget request for this Institute is $471,553,000. I shall be pleased to answer any questions.

[The statement of Dr. Kirschstein follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of General Medical Sciences

I am pleased to be here once again to present the programs of the National Institute of General Medical Sciences. These programs which support basic, untargeted biomedical research endeavors will continue to provide the knowledge through which specific diseases can be conquered. This ability to develop basic concepts and to rapidly translate the knowledge so generated into leads regarding those many diseases not yet understood has been telescoped from years to often only months. Yet, as each question is answered, new ones arise. What is clear is that progress builds on progress, and the future holds great promise for continuing advances. It is toward this future that the fundamental biomedical research and research training efforts supported by the National Institute of General Medical Sciences are aimed.

Nowhere is this natural flow of research endeavors from fundamental undifferentiated studies to disease-targeted activities better illustrated than by an account of the work of Drs. Michael Brown and Joseph Goldstein, this year's winners of both the Nobel Prize in Physiology or Medicine and the Lasker Award for basic medical research. Indeed, the story of the careers of Drs. Brown and Goldstein clearly demonstrates the vital role of NIH in biomedical research. Both men began their research careers in the intramural program of NIH. They then went to the University of Texas Health Science Center in Dallas, where their basic studies of cellular steroid receptors were supported by the NIGMS for a number of years. Gradually their collaborative studies focused on a particular steroid chemical, cholesterol, and they discovered a mechanism that controls its metabolism. Since such basic studies of cholesterol are critical to an understanding of, and the development of treatment regimens for, atherosclerosis and other cardiovascular disease, their research, originally supported by NIGMS, has been supported by the National Heart, Lung, and Blood Institute in recent years. Dr. Lenfant and I are pleased to thus illustrate the importance of all units of NIH in the continuum of biomedical research activities.

Pharmacological Sciences Program - Biorelated Chemistry

A field which has greatly contributed to our fundamental biomedical knowledge is chemistry. In 1985, the National Academy of Sciences (NAS) published a survey of Opportunities in Chemistry in which it outlined the past contributions of this field and the future advances which may lead to better health. As stated in the NAS report:

> Chemistry in the next decade will contribute to the solution of some of contemporary biology's most important problems. . . . Ultimately, our ability to control complex biological events will depend upon understanding at the molecular level. . . . Chemistry research relevant

to the NIH mission concentrates largely in the National Institute of General Medical Sciences.

Much research in chemistry involves efforts to relate the physical and chemical behavior of organic compounds to their molecular structure. It deals with the pathways by which chemical reactions occur. Over the years, the NIGMS has supported many chemists working in this area, including Nobel Laureates Drs. Herbert Brown, Roald Hoffmann, and Henry Taube. All of them helped to elucidate chemical reactions which are of importance to both health-related areas and industry.

Another significant area of chemistry is the synthesis of biologically important and useful substances which lead to products of far greater purity than can be obtained by starting with natural materials. Such synthesis has led and will lead, with even greater rapidity, to the development of new and more active therapeutic agents. For example, a chemist at the University of California in Berkeley has developed more efficient and direct methods for the total laboratory synthesis of steroids, a class of compounds that includes the anti-inflammatory agent, cortisone, and sex hormones, such as estrogen and progesterone. Steroids are chemicals in which atoms are arranged in a complex cyclic configuration. The team at Berkeley, using chemicals containing metals such as cobalt, has achieved the ability to catalyze or speed up the assembly of the needed atoms in cyclic fashion, directly and efficiently. This approach has been shown to be very versatile and is being used industrially to produce vitamin B_6 (a vital dietary constituent), as well as various pharmacologically active cyclic compounds, such as synthetic estrogens and corticosteroids.

Genetics Program

Another chemist, Dr. Jacqueline Barton of Columbia University, is designing molecules that can recognize and insert themselves into specific sites of the deoxyribonucleic acid (DNA) molecule, thus changing its structure. This may lead to the development of new cancer chemotherapeutic agents as well as a greater understanding of gene expression.

Identification of specific sites of expression of particular genes has permitted researchers to alter these genes, using a method called "site- directed mutagenesis." This technique first involves a determination of the sequence of the nucleotide building blocks of the gene being studied. Next, copies of these sequences are synthesized in the laboratory, except that each copy has a small altered fragment which causes a change, or mutation, at a specific site. These altered sequences are then combined with the host DNA, using recombinant DNA technology. What this does is to replace a normally occurring genetic instruction with another which is man-made. This new instruction may be designed to produce a specific protein--one which geneticists can tailor to particular requirements, for example, for the production of therapeutic products which may serve as anti-viral or anti-cancer agents.

Biophysics and Physiological Sciences Program

Furthermore, site-directed mutagenesis has been used extensively by biophysicists to test their theories as to the relationship of the structure of a particular protein to its function. If a mutation is produced at a single specific site on the gene coding for a protein, an altered protein is produced. Biophysicists thus can determine the relation of the altered protein structure to abnormal function; for example, the abnormal hemoglobin present in sickle cell disease or thalassemia.

This methodology is but one of a number of new techniques which, like highly sophisticated research instruments, have been developed by NIGMS grantees in order to permit the scientific advances which we have called the "biological revolution." Among these are rapid DNA sequencing, the chemical synthesis of nucleotide sequences, methods to isolate very large DNA fragments, as well as computer programs to identify these segments. Another new technique, two-dimensional nuclear magnetic resonance, has the potential to determine the positions of specific atoms in large molecular complexes of proteins and nucleic acids, which are the very "stuff of life."

Cellular and Molecular Basis of Disease Program

Scientists use these techniques, X-ray crystallography, recombinant DNA technology, and site-directed mutagenesis, along with disciplines such as chemistry and genetics, to gain more and more understanding of how the cell functions. What stands out is the dramatic expansion of the use of all these tools to learn about the organization of cells into tissues and organs. Fundamental questions still exist about how a multicellular organism develops. What is the time sequence of developmental events? How are they controlled? How do individual cells coordinate their behavior so that each plays its proper role at the proper time?

Recently, and very surprisingly, it has become clear that some answers to these questions may come from studies of groups of single-cell organisms, bacteria. It turns out that a certain type of bacteria called Myxobacteria undergoes, during its life cycle, primitive differentiation by single cells coming together into a multicellular form and that this is based on the exchange of chemical signals between the cells. These important studies by Dr. Martin Dworkin of the University of Minnesota and Dr. A. D. Kaiser of Stanford University, among others, make use of the remarkable genetic, biochemical, and molecular manipulations and analyses that are possible today, in order to determine what intercellular chemical signals are needed to coordinate the development and differentiation of the multicellular state. By making mutants of Myxobacteria and using recombinant DNA technology, Dr. Kaiser has been able to find that certain chemicals are required and must be available to all the individual bacterial cells in order for multicellular development and differentiation to take place. If the chemicals are not available to the mutant bacterial cells, such development is inhibited. Dr. Kaiser has found that this simple bacterial model is very easily manipulated and may well become the first system of multicellular development to be fully understood in terms of genetic and molecular mechanisms.

Research Training

It is abundantly clear that fundamental research is a most remarkable endeavor and one which is very rapidly providing answers to critical problems of health and disease. This enormous leap forward through the development of new technologies and instrumentation has been made possible by the creativity and continuum of endeavors of a broad spectrum of researchers. The NIGMS research training programs have had a very large role in the preparation of superb scientists at universities throughout the country, scientists who have made, and are continuing to make, important advances both in untargeted basic research and in targeted studies such as those now being done by Drs. Brown and Goldstein, this year's Nobel Laureates. Indeed, while many NIGMS research grantees were supported under the Institute's research training programs, about one-half of those supported in NIGMS predoctoral training programs now are doing research which is supported by other, categorical institutes of NIH. Furthermore, as you know, a study by the National Academy of Sciences has shown that the young men and women trained in NIGMS-supported predoctoral programs have been more productive scientists than are those who did not receive NIH research training support. Of particular note is the Medical Scientist Training Program, which provides students with research training for the combined M.D.-Ph.D. degree. Individuals with this combined degree are among the most successful in obtaining research grant support from NIH.

Minority Access to Research Careers Program

One specialized training program about which I have told this Committee in past presentations is the Minority Access to Research Careers (MARC) Program. I am pleased to tell you that this year an evaluation of the MARC Honors Undergraduate Research Training Program has been completed by the National Academy of Sciences Committee on National Needs for Biomedical and Behavioral Research Personnel. The study found that MARC honors students are talented and highly motivated and that many of them would have been unable to finish their college curriculums without support from the MARC Program. Seventy-six percent of the MARC trainees who have graduated are enrolled in advanced graduate or professional studies. The percentage of biology majors at schools which have MARC Honors Programs has increased, and there are higher rates of bachelor's degrees earned in biology than previously. I have copies of this report available for members of the Committee.

I hope that I have conveyed some of the excitement of the advances in fundamental biomedical research, which are continuing to have an enormous impact on our understanding of ways to maintain and improve the health of the people of the world. The pace of discovery has been increasing but is far from its peak. There is so much yet to learn. The programs of NIGMS are aimed at providing the research manpower to keep up the momentum and at advancing knowledge of the fundamental cellular, molecular, chemical, and genetic processes so essential to developing better ways to prevent and treat disease.

Mr. Chairman, the 1987 budget request for this Institute is $471,533,000. I shall be pleased to answer any questions.

KIRSCHSTEIN, DR. RUTH L.
Director, National Institute of General Medical Sciences

October 12, 1926. Brooklyn, New York

Education: A.B., magna cum laude, Long Island University, 1947. M.D., Tulane University School of Medicine, 1951.

Professional History: 1951-52, Internship, Medicine and Surgery, Kings County Hospital, Brooklyn, N.Y. 1952, Assistant Resident, Pathology, Veterans Administration Hospital, Chamblee, Ga. 1952-54, Resident, Pathology, Providence Hospital, Detroit, Mich. 1954-55, Trainee of National Heart Institute and Instructor in Pathology, Tulane University School of Medicine. 1956-57, Medical Officer, Resident in Pathology, Clinical Pathology, Clinical Center, NIH. 1957, Medical Specialty Board Certification, Pathology (anatomic and clinical pathology). 1957-60, Medical Officer, Pathologist, Laboratory of Viral Products, DBS, NIH. 1960-62, Chief, Section of Pathology, Laboratory of Viral Immunology, DBS, NIH. 1962-64, Assistant Chief, Laboratory of Viral Immunology and Chief, Section of Pathology, DBS, NIH. 1964-65, Acting Chief, Laboratory of Pathology, DBS, NIH. 1965-72, Chief, Laboratory of Pathology, DBS, NIH. 1971-72, Assistant Director, Division of Biologics Standards, NIH. 1972-73, Acting Deputy Director, Bureau of Biologics, FDA. 1973-74, Deputy Associate Commissioner for Science, FDA. 1974-present, Director, National Institute of General Medical Sciences, NIH.

Professional Organizations: American Association of Immunologists; American Association of Pathologists; American Society for Microbiology; Institute of Medicine, National Academy of Sciences.

Committee Memberships: Invited member of World Health Organization Expert Group on International Requirements for Biological Substances; Geneva, Switzerland, 1965 and 1971. Invited consultant to World Health Organization concerning problems related to the use of Poliovirus Vaccine, Live, Oral; Geneva, Switzerland, 1967. Member, Primate Research Centers Advisory Committee, Division of Research Resources, NIH, 1971-1975. Member, National Commission on Diabetes, 1975. Member, National Commission on Arthritis and Related Musculoskeletal Diseases, 1975. Chairperson, NIH Grants Peer Review Study Team, 1975-1976. Chairperson, PHS Genetics Coordinating Committee, 1976-1979. Member, Fogarty International Center Scholars-in-Residence Advisory Committee, 1977-1982. Member, NIH Coordinating Committee on Manpower, 1978-1983. Chairperson, PHS Task Force on Women's Health Issues, 1983-1984. Chairperson, PHS Coordinating Committee on Women's Health Issues, 1984-present. Member, NIH Advisory Committee for the IOM Study of the Organizational Structure of the NIH, 1983-1984. Member, HHS Executive Development Board, 1985-present.

Honors, Awards: Elected to Institute of Medicine, National Academy of Sciences, 1982. Doctor of Science, Honoris Causa, The Mount Sinai School of Medicine, 1984. Honorary Doctor of Laws, Atlanta University, 1985. DHEW Superior Service Award, 1971. PHS Superior Service Award, 1978. Presidential Meritorious Executive Rank Award, 1980. PHS Equal Opportunity Achievement Award, 1983.

PHS Special Recognition Award--group award to PHS Task Force on Women's Health Issues (Dr. Kirschstein, Chairperson), 1985. Distinguished Executive Service Award of the Senior Executive Association, 1985. Presidential Distinguished Executive Rank Award, 1985.

MANDATING NUMBER OF GRANT AWARDS

Mr. **Natcher**. Thank you very much, Dr. Kirschstein.

Now, you have been at NIH some time, and you have appeared before our committee on many occasions. You are familiar with last year's controversy over the number of research grants to be funded out of the 1985 appropriations.

You know that in response to the proposal to stretch a portion of the 1985 appropriation over two years, thereby reducing the number of grants to be funded, the committee was forced to specify the number of competing grants at 6200 in appropriation language.

In the 1986 Act, we felt that we had to do this again. Now, we have before us a proposal to eliminate the legislative requirement to fund no fewer than 6100 competing grants in 1986.

We also have before us a budget proposal to include in the 1987 bill a requirement that no fewer than 19,400 competing and non-competing awards be funded by NIH and the Alcohol, Drug Abuse and Mental Health Administration in 1987.

Dr. Kirschstein, tell us, if you will, please, how you feel about the advantages and disadvantages of including, number one, the number of competing research grants or, number two, the total number of grants, competing and non-competing, in the Appropriations Act.

How do you feel about it, Doctor?

Dr. **Kirschstein**. Mr. Chairman, the new stabilization policy of the Department, which would specify the total number of research grants rather than specifying the number specifically for new and competing research grants would provide some needed stability for the research community.

However, there would be some fluctuation from year to year in the number of new and competing grants. Dependent on which particular year an individual applied for a new or a competing renewal grant such a fluctuation might affect that particular individual, either adversely or positively.

Overall, however, I think that knowing that there will be stabilization of the total number of grants could have a very positive effect.

Mr. **Natcher**. Thank you, Dr. Kirschstein. Last year this subcommittee decided the way to handle this bill as far as NIH is concerned is to put in enough money in the bill and then fix the number, as far as new grants are concerned. This was our idea.

MERIT AWARD

Dr. Kirschstein, describe the new Merit Award.

Dr. **Kirschstein**. The new mechanism that NIH proposes, called the Merit Award, is an award for a reserach project to very meritorious investigators, which would provide between 5 and 10 years of support for such individuals as a result of a recommendation made by the advisory council of each particular Institute.

It would be a mechanism by which well-known, established investigators could receive longer periods of support than they do currently in order to allow them to continue to do highly meritorious research without having to be concerned about making applications at repeated short intervals.

Mr. NATCHER. Thank you.

What are the reasons for creating this new type of award at this particular time, Doctor?

Dr. KIRSCHSTEIN. The proposal to create a Merit Award is an NIH initiative and I will give you my comments on it, and then perhaps Dr. Wyngaarden might like to add his.

I believe the reasons for creating or planning such an award relate to discussions that were held a year or so ago, at the NIH Director's Advisory Committee, which met to consider the length of research grants and the entire peer review system.

This Committee felt that there ought to be a mechanism by which established highly meritorious investigators could continue their research endeavors, and expand their horizons without having to reapply for grant support every three or so years.

This would give such investigators a feeling of stability and an opportunity to undertake some projects that they might not otherwise consider doing.

Dr. WYNGAARDEN. We did examine the entire extramural award system. We looked at three major issues; that is, the matter of the first-time investigator, the mid-career investigator, and those having very high productivity, as well as other ways in which we could make the system more efficient, that is, the whole process of review at the study section and council level. The Director's Advisory Committee agreed with our concerns and made some recommendations, and this proposed Merit Award grew out of that conference. This is a device to provide longer-term support for exceptional mid-term scientists. The scientists that would be eligible would have at least three awards from us, over a 10-year period and have been doing research in the very high priority area. It must also be the judgment of the council that their research would be likely to be highly productive for some period into the future. The award would be made in two parts, for up to a 10-year award. Mechanically, it would be viewed as two consecutive awards with less than the usual requirements laid on the investigator during the renewal process.

For example, in the fourth year, the investigator would file a summary progress report rather than a voluminous re-application, and if everything was still highly satisfactory, that person would receive, in effect, an extension. It would be counted as a competing renewal grant, however, so our commitment base, namely the number of extant awards, would not grow out of control.

This would have almost no effect on the commitment base, but would simplify the procedure for those individuals who undoubtedly will be approved anyway.

Mr. NATCHER. Will all Institutes make these awards?

Dr. WYNGAARDEN. Yes.

Dr. KIRSCHSTEIN. Yes, sir.

Mr. NATCHER. How many such awards will be made?

Dr. KIRSCHSTEIN. The award mechanism has not yet been implemented, and specific guidelines, I think, are in the process of being developed.

I would anticipate that there would be very few awards made during the first or second year, and that NIH would gradually award a more significant number as time goes by.

We anticipate that the advisory councils will probably look at these awards very carefully.

As the National Institute of General Medical Sciences has been planning for such awards, it is the feeling of its advisory council that the investigators to be considered for such awards, should have had previous NIGMS support for at least 10 years.

NEGOTIATED DIRECT COST REDUCTIONS

Mr. NATCHER. The budget, as you know, requires negotiated reductions in direct costs of noncompeting and competing research grants in both 1986 and 1987.

How large, percentage-wise, will these reductions be in research projects funded by your Institute?

Dr. KIRSCHSTEIN. For non-competing awards, at the FY 1986 sequestration level the reductions will be approximately 6 percent of the direct costs. For competing awards, these reductions will be approximately 9 percent. In FY 1987, these reductions would average 12 percent for noncompeting and 11 percent for competing awards. We are, however, looking at these awards and discussing them individually with grantees in an attempt to take into consideration factors that perhaps we at NIH don't know about that may be of particular concern.

Mr. NATCHER. Some Institute Directors have advised us that rather than making negotiated reductions in excess of 10 percent, it would be better not to make a grant at all. Do you agree with that, Doctor?

Dr. KIRSCHSTEIN. There is no question that once one begins to have to negotiate more than 10 percent below the very carefully determined budget for a grant—a budget that the initial review group or study section has put together—there will be a serious adverse effect on the work that an investigator is able to do.

It may require that fewer personnel be used. There may be supplies that cannot be provided. So it is correct to say that it would be very difficult for grantees to deal with budget cuts of 10 percent or more.

COMMENTS FROM PRESIDENT'S SCIENCE ADVISOR

Mr. NATCHER. Dr. Kirschstein, last year when we were in the middle of the controversy over the program level for competing research grants for fiscal year 1985, a letter signed by the President's Science Advisor appeared in the May 30 issue of the *New England Journal of Medicine,* which seems to have been written as a defense of the budget proposal to fund 5,500 competing research grants in 1985, instead of the 6,500 which Congress thought it had approved.

Our committee members have been here long enough, as you know, Doctor, to know that documents written in defense of budget proposals most times must be taken with a grain of salt.

However, this letter is in a different category, because, one, it is signed by the President's Science Advisor; two, it appeared in one of our most prestigious scientific journals; and three, it casts doubt on the quality of the research sponsored by NIH.

Some of the allegations made in the letter are that, (1) the concentration on the number of competing awards prevents funding projects for a longer period, such as five to seven years.

(2) The emphasis on competing projects discourages funding of other mechanisms such as specialized centers of research.

(3) Congressional earmarking diverts large chunks of the NIH budget from more scientifically promising endeavors.

(4) 25 percent of the NIH budget is directed by Congress toward specific diseases, projects and programs, many of which are funded even though they have quite poor scientific ratings.

(5) Excessive Congressional directives are undermining peer review.

Dr. Kirschstein, do you think there is merit in any of these allegations? And if so, Doctor, tell us which ones, or one. Pick out any one of them, Doctor.

Dr. KIRSCHSTEIN. Mr. Chairman, I think that the record of NIH speaks for itself, and particularly the record of the National Institute of General Medical Sciences. I have been delighted over the 12 years that I have been the Director of NIGMS that the members of this committee have understood full well the importance of the fundamental undifferentiated, untargeted research that NIGMS supports, and have realized that this type of research is absolutely essential as an underpinning for all the activities of the other Institutes.

The research supported by this Institute is of excellent quality, and the research applications that we receive are truly excellent. Indeed, we cannot, at the moment, under the exigencies of the budget—which I fully understand—support all of the excellent, important, fundamental research which seeks NIGMS support.

Mr. NATCHER. All right.

Mr. Conte, I yield to you.

RESEARCH AREAS AFFECTED BY CUTS

Mr. CONTE. Doctor, it is good to have you here again, and my congratulations as well for receiving a Presidential award for distinguished service.

I was down at the Department the other day, and there was a big poster with your picture on it announcing the award. Obviously they are proud of you, and so are we.

Doctor, looking at this chart I have here, under the revised budget request for fiscal year 1986, you would lose about 170 competing grants from the level funded in fiscal year 1985, and you would lose an additional 130 in fiscal year 1987. That is a decrease of 300 competing grants in two quick years.

What areas of research would be hardest hit by this kind of cut, and what possible repercussions will it have for our research efforts in the years to come?

Dr. KIRSCHSTEIN. The decreases you mention would be felt in all our programs. However, since about two-thirds of the research grants that we award are in the Institute's cellular and molecular basis of disease and genetic program—two areas where the science is moving very rapidly—those are the areas that would be hurt the most.

DOLLARS NEEDED FOR COMPETING AWARDS

Mr. **Conte**. How much would we need to add to your 1987 request for new and competing grants to keep you at a level equivalent to the one this subcommittee fought so hard for in 1985?

Dr. **Kirschstein**. Since the Institute's FY 1987 budget provides for 689 new and competing awards, compared to 987 in FY 1985 we are short about 298 new and competing awards.

Mr. **Conte**. How many millions?

Dr. **Kirschstein**. An additional 298 new and competing awards, awards which will require $48 milion more.

Mr. **Conte**. $48 million?

Dr. **Kirschstein**. Yes.

ELIMINATION OF RESEARCH CENTER GRANTS

Mr. **Conte**. The justifications show that you will lose one research center grant to the Gramm-Rudman-Hollings sequestration in fiscal year 1986, and an additional four under the budget request for fiscal year 1987.

What centers does the Institute currently support, and which ones would be eliminated in 1986 and 1987?

Dr. **Kirschstein**. We support research center grants in a number of areas, pharmacological sciences, anesthesiology, burn and trauma research, genetics, and molecular pathology, the latter being the cellular and molecular basis of disease program.

In FY 1986, the Institute will eliminate a genetics research grant. In 1987, under the President's request, one center in pharmacological sciences, one in burn and trauma research, and one in genetics would be eliminated.

Mr. **Conte**. Are these centers a particularly low priority of the Institute?

Dr. **Kirschstein**. The highest priority of an Institute such as NIGMS is to support individual investigator-initiated research grants, the activity in which this committee has been particularly interested. There are, however, certain important aspects of the research center grants that our Institute supports that we think are important. The research centers that we support take the fundamental research that is done through the individual research grants, and bring it closer to the clinical arena.

They are bridging grants; to a great extent they bridge the gap between basic research and clinical research.

In the burn and trauma research centers, this is particularly important, because of the need to apply what we have learned about the fundamental body injuries and the total body response to burn and trauma. It is important to apply this to patients and sometimes important discoveries come out of such research. For example, at the Burn and Trauma Center at the Massachusetts General Hospital, under Drs. Burke and Yannas, the very important artificial skin was developed, and is now being used in eight burn centers throughout the country.

Mr. **Conte**. That center would be closed?

Dr. **Kirschstein**. That is one of the centers that could be affected.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
Summary by Mechanism
(In thousands)

			1986							
	1985 ACTUAL OBLIGATIONS 2/		APPROPRIATION 1/ 2/		AVAILABLE AFTER SEQUESTRATION 2/		REVISED 2/		1987 REQUEST 2/	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:										
Noncompeting	12000	$1,805,610	12576	$2,056,145	12576	1,967,708	12576	$1,967,685	12785	$2,003,507
Admin. supp.	(580)	30,479	(435)	17,506	(435)	16,752	(435)	16,739	(399)	15,200
Competing	6219	915,951	6073	961,849	6073	920,976	5492	867,285	5104	784,541
Subtot., C	6219	915,951	6073	961,849	6073	920,976	5492	867,285	5104	784,541
Subtot.,RPG	18219	2,752,040	18649	3,035,500	18649	2,905,436	18068	2,851,709	17889	2,803,248
Research Ctrs:										
Spec/comp.	347	319,976	350	327,464	348	313,383	348	313,383	340	295,403
GCRC	78	86,805	78	89,896	78	86,031	78	86,031	76	86,082
Biotech	61	34,962	61	35,632	61	34,100	61	34,100	60	33,898
LASPR	46	28,869	46	30,346	46	29,041	46	29,041	46	29,905
Gorgas	1	1,999	1	1,999	1	1,913	1	1,913	1	1,934
Subtotal	533	472,611	536	485,337	534	464,468	534	464,468	523	447,222
Other Res.:										
Careers	1314	76,277	1310	79,577	1270	76,156	1271	76,156	1270	76,249
Organ sys.	1	935	1	1,000	1	957	1	957	1	800
Clin. ed.	45	3,963	52	4,700	52	4,498	52	4,498	39	2,400
Coop. cl.	287	52,618	272	52,346	245	50,095	245	50,095	256	51,876
BRS	728	95,733	720	95,500	713	91,393	713	91,393	154	32,883
MBRS	95	34,255	92	34,876	92	33,375	92	33,375	92	33,642
Other	555	44,293	547	42,066	530	40,243	531	40,243	489	39,684
Subtotal	3025	308,074	2994	310,065	2903	296,717	2905	296,717	2301	237,534
Total,RGs	21777	3,532,725	22179	3,830,902	22086	3,666,621	21507	3,612,894	20713	3,488,004
Training										
Individual	1831	41,267	1569	36,888	1473	34,544	1473	34,544	1292	30,630
Institutional	8792	176,102	8602	181,791	8474	174,733	8474	174,733	7966	167,574
Total	10623	217,369	10371	218,679	9947	209,277	9947	209,277	9258	198,204
Contracts	1172	350,963	1235	344,987	1202	330,157	1202	330,157	1192	328,458
Intramural		561,680		561,044		536,850		536,850		548,357
RM&S		214,763		212,683		203,463		203,463		210,894
Control		63,794		63,878		61,131		61,131		61,131
Construct.		13,100		8,600		8,230		8,230		---
Total, IRDs		4,954,394		5,240,773		5,015,729		4,962,002		4,835,048
Nat. Library of Med.		54,098		57,759		55,273		55,273		56,408
Office of Director		34,179		46,990		44,969		35,829		36,701
Bldg. & Facilities		15,675		14,900		14,259		14,259		8,000
		5,058,346		5,360,422		5,130,230		5,067,363		4,936,157

1/ Adjusted for $4,500 transfer to DHHS from NCI for the Mary Babb Randolph Cancer Center.

2/ The 1985 and 1986 columns have been adjusted for comparability for AIDS as follows: 1985 - $63,737; 1986 appropriation - $140,723; 1986 Gramm-Rudman - $134,672; and 1986 Revised - $120,757. The 1987 column reflects centralization of AIDS in OASH ($143,868).

NOTE: All 1986 columns have been adjusted to reflect the following: an administrative reduction of $3,000, a consultant services reserve of $4,056, and a carryover in research project grants of $11,247.

NATIONAL INSTITUTES OF HEALTH

APPROPRIATION HISTORY

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1976..........	$1,980,474,000	$2,150,755,000	$2,267,081,000	$2,302,126,000 1/
TQ............	431,905,000	429,047,000	428,618,000	439,107,000
1977..........	2,165,047,000	2,450,278,000	2,671,796,000	2,544,078,000
1978..........	2,596,077,000	2,760,236,000	2,914,369,000	2,842,936,000 2/
1979..........	2,884,720,000	2,952,191,000	3,024,316,000	3,189,976,000 3/
1980..........	3,185,928,000	3,381,030,000	3,367,757,000	3,428,935,000 4/
1981..........	3,512,320,000	3,572,427,000	3,564,765,000	3,569,406,000 5/
1982..........	3,310,985,000 6/	3,834,958,000	3,818,710,000	3,641,875,000 7/
1983..........	3,748,771,000	4,013,450,000	4,028,591,000	4,023,969,000 2/
1984..........	4,077,092,000	4,314,501,000 8/	4,322,912,000 8/	4,493,588,000 9/
1985..........	4,566,453,000	4,834,343,000 10/	5,163,597,000	5,149,985,000
1985 Proposed Rescission...	-10,448,000			
1986..........	4,852,680,000	5,247,836,000 11/	5,463,658,000	5,498,454,000
1986 Sequester.	-236,243,000			
1986 Proposed Rescission....	-76,782,000			
1987..........	4,936,157,000			

1/ Includes $123,646,000 NRSA training programs authorized under a Continuing Resolution.

2/ Includes $221,250,000 authorized under a Continuing Resolution.

3/ Authority was a Continuing Resolution.

4/ Authority was a Continuing Resolution; reflects a rescission of -$446,000,000 authorized under P.L. 96-304.

5/ Authority was a Continuing Resolution; reflects a rescission of -$47,041,000 authorized under P.L. 97-12.

6/ September budget, original request was $3,762,483,000.

7/ The 1982 Continuing Resolution was the lower of the House or Senate Allowance less a 4 percent reduction.

8/ Excludes $166,368,000 not considered.

9/ Includes $175,838,000 authorized under a Continuing Resolution.

10/ Includes $237,435,000 not considered.

11/ Excludes $217,943,000 not considered.

Department of Health and Human Services
National Support for Performance of Medical and Health-Related R&D, by Source of Funds, 1979-1985[1]

(Millions of Dollars)

Source of Funds	1979	1980	1981	1982	1983	1984 est.	1985 est.
Total	$7,113	$7,914	$8,540	$9,239	$10,208	$11,533	$12,823
Government	4,721	5,145	5,340	5,527	5,971	6,684	7,473
Federal	4,321	4,723	4,848	4,970	5,399	6,082	6,847
NIH	2,953	3,182	3,333	3,433	3,789	4,252	4,824
State & local	400	422	492	557	572	602	626
Industry[2]	2,093	2,456	2,875	3,373	3,887	4,486	4,973
Private nonprofit	299	313	325	339	350	363	377
Foundations	60	54	52	44	41	38	36
Vol. health agencies	131	148	160	177	186	196	206
Other	108	111	113	118	123	129	135

[1] Excludes research training and construction. Includes U.S.-funded health R&D support spent abroad. Updated 1984-1985 and estimated 1986 figures will be available in Summer 1986.

[2] Revised 1985.

Note: Federal data are obtained via an interagency survey conducted by the National Institutes of Health. Estimates for State and local governments include awards made by governmental agencies, as well as appropriations made to educational institutions for the performance of health R&D. The industry sector includes data for the pharmaceutical, medical supply, and biomedical engineering industries. The non-industrial private sector covers the funds provided by philanthropic foundations, voluntary health agencies, and other private contributors for the support of health R&D.

Program Analysis Branch
DPA/OPPE/OD/NIH
February 7, 1986

Department of Health and Human Services

NATIONAL INSTITUTES OF HEALTH

Year-End Status of Extramural Programs

RESEARCH PROJECT GRANTS

(Amount in thousands)

	1985		1986 APPROPRIATION		1986 APPROPRIATION AFTER SEQUESTRATION		1986 REVISED		1987 REQUEST	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
NCI:										
Funded	2992	$516,475	3082	$589,143	3082	$563,970	3008	$557,170	2924	$537,134
Unfunded	1774	255,100	2180	355,139	2180	362,534	2254	369,334	2393	445,998
NHLBI:										
Funded	2638	479,165	2708	533,734	2708	510,811	2639	499,342	2605	498,906
Unfunded	1547	203,699	1637	229,739	1637	236,694	1706	248,163	1883	304,994
NIDR:										
Funded	397	47,127	397	47,009	397	44,991	397	44,991	379	43,244
Unfunded	187	20,727	199	26,503	199	27,277	199	27,277	242	36,327
NIADDK:										
Funded	2035	294,814	2044	319,943	2044	306,297	1971	299,841	1927	291,143
Unfunded	1030	113,255	1184	143,876	1184	147,947	1257	154,403	1329	180,881
NINCDS:										
Funded	1866	257,534	1919	294,273	1919	281,619	1871	272,065	1851	269,735
Unfunded	1186	169,747	1592	232,514	1592	237,036	1640	246,590	1851	310,264
NIAID:										
Funded	1715	245,266	1724	257,323	1724	246,282	1662	244,769	1599	229,943
Unfunded	955	106,254	1089	139,532	1089	142,826	1151	145,930	1155	158,791
NIGMS:										
Funded	2894	396,833	2943	429,695	2943	411,268	2781	403,910	2771	394,079
Unfunded	1216	134,955	1363	161,423	1363	167,341	1525	175,856	1557	201,459
NICHD:										
Funded	1367	187,604	1374	199,211	1374	190,665	1358	189,515	1369	189,631
Unfunded	1193	136,238	1281	157,507	1281	160,396	1297	160,796	1395	185,336
NEI:										
Funded	1068	133,224	1141	149,415	1141	142,994	1114	137,770	1103	137,261
Unfunded	379	40,457	299	38,783	299	40,803	326	43,993	449	64,651
NIEHS:										
Funded	342	52,632	358	56,632	358	54,197	358	54,197	334	52,913
Unfunded	226	28,749	252	32,810	252	33,538	252	33,538	312	45,554
NIA:										
Funded	478	81,671	504	92,700	504	88,771	480	86,092	490	84,248
Unfunded	400	56,409	381	58,002	381	59,340	405	62,019	434	73,530
NIAMSD:										
Funded	565	77,554	582	83,599	582	80,030	556	78,506	537	75,011
Unfunded	371	43,156	429	55,923	429	57,070	455	58,594	506	71,002
TOTAL:										
Funded	18357	2,769,899	18776	3,052,677	18776	2,921,895	18195	2,868,168	17889	2,803,248
Unfunded	10464	1,308,746	11886	1,631,751	11886	1,672,802	12467	1,726,493	13506	2,078,787

Department of Health and Human Services

NATIONAL INSTITUTES OF HEALTH

Year-End Status of Extramural Programs
Training Programs

INDIVIDUAL AWARDS

(Amount in thousands)

	1985		1986 APPROPRIATION		1986 REVISED 1/		1987 REQUEST	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
NCI:								
Funded...........	241	$5,308	204	$4,626	195	$4,427	189	$4,292
Unfunded.........	98	2,121	102	2,247	111	2,446	197	4,596
NHLBI:								
Funded...........	210	5,191	234	6,031	217	5,772	203	5,140
Unfunded.........	89	1,780	56	1,443	73	1,942	82	2,076
NIDR:								
Funded...........	37	974	50	1,250	48	1,196	42	1,050
Unfunded.........	6	149	3	75	5	125	5	125
NIADDK:								
Funded...........	171	4,251	121	2,985	120	2,957	116	2,856
Unfunded.........	86	2,080	151	3,747	152	3,775	163	4,044
NINCDS:								
Funded...........	253	5,486	208	4,501	199	4,307	199	4,307
Unfunded.........	80	1,715	179	3,740	188	3,934	174	3,629
NIAID:								
Funded...........	75	1,849	85	2,156	69	1,722	55	1,414
Unfunded.........	152	3,292	158	4,146	177	4,698	183	4,895
NIGMS:								
Funded...........	502	10,668	345	7,678	312	6,831	194	4,484
Unfunded.........	403	8,734	529	11,458	562	12,305	658	16,279
NICHD:								
Funded...........	127	2,904	103	2,550	99	2,440	95	2,351
Unfunded.........	100	2,263	137	3,151	141	3,261	160	3,840
NEI:								
Funded...........	111	2,465	108	2,615	108	2,503	98	2,388
Unfunded.........	25	550	53	1,024	53	1,060	64	1,357
NIEHS:								
Funded...........	44	784	38	710	36	679	33	670
Unfunded.........	5	100	5	100	5	100	6	120
NIA:								
Funded...........	24	553	33	782	32	748	30	713
Unfunded.........	11	196	15	277	16	311	20	392
NIAMSD:								
Funded...........	32	743	37	920	35	881	35	881
Unfunded.........	16	350	22	543	24	582	27	678
DRR:								
Funded...........	4	91	3	84	3	81	3	84
Unfunded.........	--	---	1	28	1	28	2	56
TOTAL:								
Funded...........	1831	41,267	1569	36,888	1473	34,544	1292	30,630
Unfunded.........	1071	23,330	1411	31,979	1508	34,567	1741	42,087

1/ The 1986 Appropriation after sequestration is the same as the 1986 Revised.

Department of Health and Human Services

NATIONAL INSTITUTES OF HEALTH

Year-End Status of Extramural Programs
Training Programs

INSTITUTIONAL AWARDS

(Amount in thousands)

	1985		1986 APPROPRIATION		1986 REVISED 1/		1987 REQUEST	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
NCI:								
Funded...........	162	$25,489	145	$26,212	136	$25,085	128	$24,318
Unfunded.........	17	1,765	345	14,467	354	15,594	59	7,584
NHLBI:								
Funded...........	267	34,432	255	34,175	255	32,705	221	28,629
Unfunded.........	21	923	25	2,616	25	4,086	54	5,363
NIDR:								
Funded...........	47	3,829	49	3,312	45	3,170	45	3,312
Unfunded.........	5	446	5	432	9	960	4	484
NIADDK:								
Funded...........	54	16,324	32	17,615	23	16,757	19	16,188
Unfunded.........	20	2,291	45	5,143	54	5,907	61	6,718
NINCDS:								
Funded...........	30	7,664	11	8,652	7	8,280	17	8,280
Unfunded.........	17	1,366	21	1,535	25	1,907	27	2,078
NIAID:								
Funded...........	10	9,538	9	9,226	7	9,171	8	7,569
Unfunded.........	20	1,381	25	2,053	27	2,460	29	2,732
NIGMS:								
Funded...........	261	47,053	260	50,043	252	48,408	201	48,432
Unfunded.........	38	6,637	17	7,307	25	8,942	70	15,443
NICHD:								
Funded...........	100	10,958	95	11,351	91	10,863	88	10,749
Unfunded.........	18	1,556	26	3,120	30	3,608	39	4,680
NEI:								
Funded...........	9	2,766	3	2,616	3	2,504	2	2,388
Unfunded.........	8	1,035	7	1,065	7	1,082	8	1,382
NIEHS:								
Funded...........	42	7,718	42	7,792	42	7,457	38	7,336
Unfunded.........	7	778	5	990	5	1,325	6	1,221
NIA:								
Funded...........	10	4,058	7	4,725	5	4,522	7	4,396
Unfunded.........	3	248	7	771	9	1,145	8	1,029
NIAMSD:								
Funded...........	18	5,387	5	5,210	3	4,986	8	4,986
Unfunded.........	7	793	21	2,120	26	2,125	22	1,969
DRR:								
Funded...........	9	984	9	991	9	948	9	991
Unfunded.........	6	630	2	480	2	480	2	480
TOTAL:								
Funded...........	1019	176,200	922	181,920	878	174,856	791	167,574
Unfunded.........	107	19,849	551	42,099	598	49,621	389	51,163

1/ The 1986 Appropriation after sequestration is the same as the 1986 Revised.

DEPARTMENT OF HEALTH AND HUMAN S[illegible]VICES

NATIONAL INSTITUTES OF HEALTH

History of Congressional Action on Budget Requests for National Institutes of Health Institutes and Research Divisions 16/

	Budget Estimate to Congress	Appropriation
1933	$48,000	$48,000
1934	54,775	54,775
1935	50,000	50,000
1936	64,000	64,000
1937	64,000	64,000
1938	464,000	464,000
1939	515,000	515,000
1940	587,750	707,000
1941	712,120	711,000
1942	705,000	700,000
1943	1,278,270	1,278,270
1944	1,291,000	2,555,020
1945	2,835,000	2,835,000
1946	2,078,000	3,414,700
1947	10,799,500	8,125,448 1/
1948	22,403,000	28,876,000
1949	45,701,460	37,668,000
1950	40,567,000	50,167,000
1951	49,845,000	47,334,750 3/
1952	53,386,000	52,447,291
1953	55,005,000	59,030,750
1954	56,340,000	71,153,000
1955	71,128,000	81,268,000
1956 5/6/	90,023,000	98,458,000
1957	126,725,000 7/	183,007,000
1958	190,183,000	211,183,000
1959	211,814,000	294,383,000
1960	294,279,000	400,000,000
1961	400,000,000	560,000,000 8/
1962	583,000,000	738,335,000 9/
1963	780,400,000	880,800,000
1964	930,454,000	918,454,000
1965	956,492,000	965,992,000
1966 10/	1,105,006,000	1,138,406,000
1967	1,231,764,000	1,306,983,000
1968 11/	1,152,250,000	1,143,424,000
1969	1,188,293,000	1,100,092,000
1970	1,064,870,000 12/	1,122,718,400 13/
1971	1,099,249,000	1,196,249,000
1972 14/	1,333,916,000	1,476,046,000
1973 15/	1,483,982,000	1,713,455,000
1974	1,531,776,000	1,744,554,000 17/
1975	$1,785,922,000	$2,043,721,000
1976 18/	2,349,413,000	2,627,845,000
1977	2,088,179,000	2,424,510,000
1978	2,456,104,000	2,720,767,000 19/
1979	2,794,623,000	3,097,138,000 20/
1980	3,111,391,000	3,360,670,000
1981	3,432,146,000	3,490,459,000 21/
1982 22/	3,239,274,000	3,563,324,000 23/
1983	3,660,945,000	3,929,843,000 23/
1984	3,980,856,000	4,374,768,000 24/
1985	4,476,524,000	5,036,344,000
1986	4,852,680,000	5,501,454,000 25/
1987	4,936,157,000	

1/ Includes $386,500 transfers.

2/ Not less than $3,000,000 was earmarked for liquidating cash; an additional $1,175,000 was used for that purpose.

3/ Excludes $3,216,250 rescinded.

4/ Excludes $131,000 for Gorgas Memorial Laboratory.

5/ Excludes $147,000 for Gorgas Memorial Laboratory.

6/ Includes $90,000 transfer.

7/ Includes $200,000 transfer from other appropriations.

8/ Includes $12,139,000 for construction of mental health-neurology research facility.

9/ Includes $1,000,000 for planning for a gerontological research facility; and $750,00 for modernization at the Rocky Mountain Laboratory, Hamilton, Montana.

10/ Includes $25,000,000 for Regional Medical Programs, $19,700,000 for Mental Health Staffing, and $20,250,000 for Heart Disease, Cancer and Stroke Program.

11/ Excludes $246,741,000 for National Institute of Mental Health. Includes $20,615,000 for Environmental Health Sciences.

12/ Excludes $7,093,000 for Office of the Director, NIH.

13/ Includes $1,348,200 supplemental.

14/ Includes $142,075,000 supplementals.

15/ Excludes DBS. Request reflects amendment.

16/ Includes only Research Institutes, excludes NLM, B&F, and OD.

17/ House allowance reflects maximum authorized. Reflects P.L. 93-192.

18/ Request reflects amendment requested for 1976 in 1977 budget submission. Estimate and appropriation includes Transition Quarter (15 month period).

19/ Continuing Resolution was Conferees Allowance. Includes supplemental of $17,834,000.

20/ Includes Continuing Resolution for items not considered in P.L. 95-482.

21/ Reflects a rescission of $46,959,000 authorized under P.L. 97-12.

22/ Reflects the September amendment, the original request was $3,680,994,000.

23/ Continuing Resolution.

24/ Includes Continuing Resolution for items not considered in P.L. 98-139.

25/ Reflects transfer of $4,500,000 to DHHS from NCI for the Mary Babb Randolph Cancer Center and an administrative reduction of $3,000,000.

NOTE: Not all amounts on this table are comparable from year to year because of changes in the content of the appropriations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Paylines for Competing Research Project Grants
Fiscal Years 1977-1987
Data Based on Raw Priority Scores

	(------	------	------	------	ACTUAL	------	------	------	------)	(------Estimate	------	------)
	1977	1978	1979	1980	1981	1982	1983	1984 1/	1985 1/	1986 Approp.2/	1986 Revised	1987
NCI..........	225	230	235	218	197	183	181	184	172	170	160	160
NHLBI.........	234	232	256	206	208	196	195	181	177	190	180	180
NIDR..........	245	255	235	230	225	213	208	210	195	220	220	190
NIDDK.........	219	223	230	221	202	180	184	175	173	170	160	160
NINCDS........	193	227	240	232	206	189	185	169	157	150	150	140
NIAID.........	181	192	233	204	178	162	166	167	159	160	150	150
NIGMS.........	182	190	227	219	193	175	170	163	165	160	160	150
NICHD.........	203	228	233	200	196	187	179	170	162	170	170	160
NEI...........	269	272	262	232	212	203	201	193	198	210	200	170
NIEHS.........	255	239	238	217	247	226	220	224	203	200	200	190
NIA...........	291	240	278	227	213	208	190	179	202	210	200	190
NIAMSD........	--	--	--	--	--	--	--	--	--	170	160	160

1/ NHLBI and NICHD use percentiles for making funding decisions and the priority scores shown are derived from the percentile score listings in an analogous manner.

2/ Paylines reflected for the 1986 Appropriation also apply to the 1986 Appropriation after sequestration.

NOTE:

1) Paylines for actual years represent the 90th percentile priority score based on the number of funded research projects. Paylines for estimated years represent the 100th percentile priority score.

2) 1983-1987 includes the Small Business Innovation Research (SBIR) grants.

3) NIAMSD established in 1986.

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1970
(DOLLARS IN THOUSANDS)

INSTITUTE	DIRECT COSTS ONLY						TOTAL COSTS					
	REPORTING YEAR APPLICATIONS				COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	REVIEWED		COUNCIL RECOMMENDED*									
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
	7,634	$319,047	5,117	$169,526	67.0	53.1	5,142	$214,822	2,580	$110,169	50.2	51.3
NCI	754	35,932	483	18,833	64.1	52.4	485	23,926	212	11,908	43.7	49.8
NHLBI	1,013	49,382	624	23,364	61.6	47.3	627	29,293	456	20,343	72.7	69.4
NIDR	243	9,133	120	4,133	49.4	45.3	120	5,554	32	1,718	26.7	30.9
NIADDKD	1,446	56,314	1,040	32,565	71.9	57.8	1,044	41,260	528	20,953	50.6	50.8
NINCDS	837	30,140	518	14,320	61.9	47.5	523	18,172	413	13,047	79.0	71.8
NIAID	862	30,861	649	19,640	75.3	63.6	652	25,240	368	14,628	56.4	58.0
NIGMS	1,254	55,297	946	32,349	75.4	58.5	948	40,290	191	12,306	20.1	30.5
NICHD	900	38,432	514	16,702	57.1	43.5	519	21,296	261	10,401	50.3	48.8
NEI	219	8,749	169	5,470	77.2	62.5	169	6,997	95	3,532	56.2	50.5
NIEHS	106	4,807	54	2,150	50.9	44.7	55	2,794	24	1,334	43.6	47.7

NOTE: In prior NIH submissions, the total eligible for funding included council recommended for approval plus carryovers from the prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1971
(DOLLARS IN THOUSANDS)

INSTITUTE	---DIRECT COSTS ONLY--- REPORTING YEAR APPLICATIONS REVIEWED				COUNCIL RECOMMENDATION RATE		***TOTAL COSTS*** TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	REVIEWED		COUNCIL RECOMMENDED*									
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
	7,579	$341,643	5,215	$180,963	68.8	53.0	5,304	$233,837	2,691	$132,960	50.7	56.9
NCI	783	42,376	540	22,394	69.0	52.8	558	28,629	330	20,027	59.1	70.0
NHLBI	1,100	60,638	718	29,241	65.3	48.2	720	36,950	446	24,429	61.9	66.1
NIDR	269	8,457	149	4,175	55.4	49.4	164	6,211	96	4,042	58.5	65.1
NIADDKD	1,284	51,597	937	29,244	73.0	56.7	940	37,742	443	18,632	47.1	49.4
NINCDS	908	35,167	569	16,947	62.7	48.2	572	21,847	371	14,636	64.9	67.0
NIAID	800	30,794	601	18,401	75.1	59.8	606	23,975	280	12,610	46.2	52.6
NIGMS	1,086	48,415	860	29,177	79.2	60.3	896	39,054	325	18,480	36.3	47.3
NICHD	1,009	49,404	587	22,776	58.2	46.1	590	28,272	235	13,082	39.8	46.3
NEI	211	9,025	171	5,506	81.0	61.0	171	7,020	115	4,786	67.3	68.2
NIEHS	129	5,770	83	3,102	64.3	53.8	87	4,137	50	2,236	57.5	54.1

NOTE: In prior NIH submissions, the total eligible for funding included council recommended for approval plus carryovers from the prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

NATIONAL INS. .TES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1972
(DOLLARS IN THOUSANDS)

INSTITUTE	DIRECT COSTS ONLY						TOTAL COSTS					
	REPORTING YEAR APPLICATIONS				COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	REVIEWED		COUNCIL RECOMMENDED*									
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
	8,596	$424,955	6,008	$228,844	69.9	53.9	6,143	$299,870	3,625	$194,184	59.0	64.8
NCI	1,087	68,845	696	33,499	64.0	48.7	749	44,809	517	34,043	69.0	76.0
NHLBI	1,167	68,099	773	36,752	66.2	54.0	777	47,085	492	33,118	63.3	70.3
NIDR	240	9,756	142	4,874	59.2	50.0	162	7,365	111	5,300	68.5	72.0
NIADDKD	1,461	63,582	1,121	37,842	76.7	59.5	1,136	49,510	647	29,817	57.0	60.2
NINCDS	954	37,245	617	18,965	64.7	50.9	617	24,483	403	18,840	65.3	77.0
NIAID	915	36,259	718	22,580	78.5	62.3	719	29,331	368	17,175	51.2	58.6
NIGMS	1,148	57,046	896	32,056	78.0	56.2	913	41,820	501	25,100	54.9	60.0
NICHD	1,118	60,679	688	28,657	61.5	47.2	707	37,760	396	21,511	56.0	57.0
NEI	288	11,068	230	7,977	79.9	72.1	233	10,406	136	6,126	58.4	58.9
NIEHS	218	12,376	127	5,642	58.3	45.6	130	7,302	54	3,154	41.5	43.2

NOTE: In prior NIH submissions the total eligible for funding included council recommeded for approval plus carryovers from the prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1973
(DOLLARS IN THOUSANDS)

INSTITUTE	DIRECT COSTS ONLY						TOTAL COSTS					
	REPORTING YEAR APPLICATIONS				COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		F U N D E D		AWARD RATE	
	R E V I E W E D		COUNCIL RECOMMENDED*									
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
	9,306	$522,916	6,631	$272,326	71.3	52.1	6,691	$355,445	2,592	$166,028	38.7	46.7
NCI	1,428	124,582	881	47,459	61.7	38.1	896	59,303	484	38,126	54.0	64.3
NHLBI	1,279	77,462	933	43,941	72.9	56.7	937	56,429	426	32,433	45.5	57.5
NIDR	252	12,625	145	5,007	57.5	39.7	152	6,755	71	2,885	46.7	42.7
NIADDKD	1,259	62,647	982	38,749	78.0	61.9	986	50,800	341	21,193	34.6	41.7
NINCDS	1,073	49,251	761	26,991	70.9	54.8	761	35,439	240	14,110	31.5	39.8
NIAID	917	39,874	723	24,864	78.8	62.4	728	32,646	281	14,470	38.6	44.3
NIGMS	1,300	67,482	1,025	40,444	78.8	59.9	1,027	52,944	334	21,680	32.5	41.0
NICHD	1,255	64,954	769	29,167	61.3	44.9	773	39,285	254	13,081	32.9	33.3
NEI	350	14,717	289	10,501	82.6	71.4	291	13,819	124	5,522	42.6	40.0
NIEHS	192	9,303	122	5,184	63.5	55.7	139	8,000	37	2,527	26.6	31.6
NIA	1	19	1	19	100.0	100.0	1	.25	—	—	0.0	0.0

NOTE: 1) In prior NIH submissions, the total eligible for funding included council recommended for approval plus carryovers from the prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

2) NIA received its first Appropriation in FY 1976. Data for FY 1973, 1974 and 1975 represent grants funded through the NICHD Appropriation.

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1974
(DOLLARS IN THOUSANDS)

INSTITUTE	---DIRECT COSTS ONLY---						***TOTAL COSTS***					
	REPORTING YEAR APPLICATIONS				COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		F U N D E D		AWARD RATE	
	R E V I E W E D		COUNCIL RECOMMENDED*									
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
	9,448	$561,532	7,061	$301,896	74.7	53.8	7,869	$437,287	4,540	$307,280	57.7	70.3
NCI	1,638	130,951	1,131	59,789	69.0	45.7	1,139	77,278	706	56,468	62.0	73.1
NHLBI	1,501	104,851	1,117	52,160	74.4	49.7	1,155	70,681	662	57,326	57.3	81.1
NIDR	256	12,453	133	5,378	52.0	43.2	155	8,078	102	7,121	65.8	88.2
NIADDKD	1,214	64,600	961	38,329	79.2	59.3	1,113	58,049	711	41,193	63.9	71.0
NINCDS	1,081	53,190	835	31,665	77.2	59.5	977	48,740	588	38,119	60.2	78.2
NIAID	915	42,886	761	26,350	83.2	61.4	814	37,726	424	22,044	52.1	58.4
NIGMS	1,135	61,707	944	38,275	83.2	62.0	1,089	57,453	579	35,972	53.2	62.6
NICHD	1,138	62,928	719	31,611	63.2	50.2	885	50,672	473	28,776	53.4	56.8
NEI	361	15,841	310	11,542	85.9	72.9	336	16,806	191	12,014	56.8	71.5
NIEHS	170	9,942	111	5,185	65.3	52.1	167	9,668	80	5,569	47.9	57.6
NIA	39	2,183	39	1,612	100.0	73.9	39	2,136	24	2,677	61.5	125.3

NOTE: 1) In proir NIH submissions, the total eligible for funding included council recommended for approval plus carryovers from the prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

2) NIA received its first Appropriation in FY 1976. Data for FY 1973, 1974 and 1975 represent grants funded through the NICHD Appropriation.

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1975
(DOLLARS IN THOUSANDS)

INSTITUTE	DIRECT COSTS ONLY						TOTAL COSTS					
	REPORTING YEAR APPLICATIONS				COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	REVIEWED		COUNCIL RECOMMENDED*									
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
	10,096	$619,658	7,510	$331,394	74.4	53.5	7,702	$446,661	4,663	$298,328	60.5	66.8
NCI	1,874	147,575	1,333	69,594	71.1	47.2	1,343	91,738	850	69,214	63.3	75.4
NHLBI	1,531	108,486	1,137	55,545	74.3	51.2	1,141	73,729	629	44,826	55.1	60.8
NIDR	381	16,302	224	7,897	58.8	48.4	237	11,115	172	8,271	72.6	74.4
NIADDKD	1,280	75,335	999	44,291	78.0	58.8	1,005	58,599	606	37,964	60.3	64.8
NINCDS	1,009	52,469	761	28,986	75.4	55.2	762	38,496	510	27,236	66.9	70.7
NIAID	971	47,442	818	30,676	84.2	64.7	821	40,807	404	23,193	49.2	56.8
NIGMS	1,247	71,763	1,024	42,219	82.1	58.8	1,089	57,827	675	39,195	62.0	67.8
NICHD	1,059	57,302	666	28,734	62.9	50.1	706	40,831	464	28,036	65.7	68.7
NEI	311	15,377	277	10,937	89.1	71.1	295	15,102	223	10,688	75.6	70.8
NIEHS	197	12,649	119	5,641	60.4	44.6	151	8,863	87	5,711	57.6	64.4
NIA	236	14,958	152	6,874	64.4	46.0	152	9,555	43	3,995	28.3	41.8

NOTE: 1) In prior NIH submissions, the total eligible for funding included council recommended for approval plus carryovers from the prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

2) NIA received its first Appropriation in FY 1976. Data for FY 1973, 1974 and 1975 represent grants funded through the NICHD Appropriation.

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1976
(DOLLARS IN THOUSANDS)

INSTITUTE	DIRECT COSTS ONLY						TOTAL COSTS					
	REPORTING YEAR APPLICATIONS				COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	REVIEWED		COUNCIL RECOMMENDED*									
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
	10,119	$678,745	7,231	$352,952	71.5	52.0	7,258	$471,518	3,464	$263,002	47.7	55.8
NCI	2,014	181,666	1,358	86,858	67.4	47.8	1,359	113,818	674	68,187	49.6	59.9
NHLBI	1,615	118,485	1,192	61,893	73.8	52.2	1,195	82,139	707	51,123	59.2	62.2
NIDR	348	16,214	180	6,529	51.7	40.3	180	8,801	95	4,904	52.8	55.7
NIADDKD	1,207	74,168	895	41,411	74.2	55.8	895	55,159	447	30,857	49.9	55.9
NINCDS	979	54,582	690	29,000	70.5	53.1	690	39,382	234	17,370	33.9	44.1
NIAID	846	45,073	675	27,901	79.8	61.9	675	37,554	181	14,957	26.8	39.8
NIGMS	1,323	81,320	1,056	45,802	79.8	56.3	1,057	61,509	630	41,116	59.6	66.8
NICHD	1,037	62,595	685	31,418	66.1	50.2	687	41,989	267	19,891	38.9	47.4
NEI	296	15,470	249	10,583	84.1	68.4	249	14,069	161	8,922	64.7	63.4
NIEHS	229	14,015	123	5,518	53.7	39.4	124	8,068	38	3,549	30.6	44.0
NIA	225	15,157	128	6,039	56.9	39.8	147	9,033	30	2,127	20.4	23.5

NOTE: 1) In prior NIH submissions, the total eligible for funding included council recommended for approval plus carryovers for the prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

2) NIA received its first Appropriation in FY 1976. Data for FY 1973, 1974 and 1975 Represent grants funded through the NICHD Appropriation.

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1977
(DOLLARS IN THOUSANDS)

INSTITUTE	DIRECT COSTS ONLY						TOTAL COSTS					
	REPORTING YEAR APPLICATIONS				COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	REVIEWED		COUNCIL RECOMMENDED*									
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
	13,305	$951,305	9,852	$511,118	74.0	53.7	9,940	$686,848	3,840	$306,897	38.6	44.7
NCI	2,603	228,666	1,740	106,883	66.8	46.7	1,741	141,462	658	65,094	37.8	46.0
NHLBI	2,180	186,485	1,600	98,509	73.4	52.8	1,602	128,400	729	64,797	45.5	50.5
NIDR	414	22,415	230	9,773	55.6	43.6	245	14,050	107	6,795	43.7	48.4
NIADDKD	1,817	118,683	1,431	69,293	78.8	58.4	1,443	93,395	641	45,011	44.4	48.2
NINCDS	1,217	75,350	879	39,519	72.2	52.4	882	53,728	235	17,482	26.6	32.5
NIAID	1,172	65,362	969	41,888	82.7	64.1	971	57,637	268	19,499	27.6	33.8
NIGMS	1,599	105,681	1,356	63,399	84.8	60.0	1,356	84,764	446	34,316	32.9	40.5
NICHD	1,263	82,910	869	43,863	68.8	52.9	873	59,694	290	22,537	33.2	37.8
NEI	459	26,307	393	18,378	85.6	69.9	394	24,585	218	14,351	55.3	58.4
NIEHS	255	18,068	195	10,850	76.5	60.1	210	15,470	116	8,530	55.2	55.1
NIA	326	21,378	190	8,763	58.3	41.0	223	13,661	132	8,485	59.5	62.1

NOTE: In prior NIH submissions, the total eligible for funding included council recommended for approval plus carryovers from the prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. as a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1978
(DOLLARS IN THOUSANDS)

INSTITUTE	DIRECT COSTS ONLY						TOTAL COSTS					
	REPORTING YEAR APPLICATIONS				COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	REVIEWED		COUNCIL RECOMMENDED*									
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
	14,500	$1,034,295	11,249	$589,198	77.6	57.0	11,489	$819,711	5,200	$420,850	45.3	51.3
NCI	2,663	240,245	2,033	126,340	76.3	52.6	2,042	170,367	886	91,035	43.4	53.3
NHLBI	2,129	165,430	1,595	92,045	74.9	55.6	1,625	130,644	759	67,553	46.7	51.8
NIDR	512	30,126	331	16,073	64.6	53.4	365	23,643	144	10,306	39.5	43.6
NIADDKD	2,018	139,323	1,614	79,991	80.0	57.4	1,627	108,961	685	52,241	42.1	47.9
NINCDS	1,271	76,742	995	44,063	78.3	57.4	1,008	61,158	534	35,522	53.0	58.1
NIAID	1,255	76,445	1,086	52,260	86.5	68.4	1,091	71,420	397	31,059	36.4	43.5
NIGMS	1,880	121,492	1,611	77,459	85.7	63.8	1,686	111,461	788	58,232	46.7	52.2
NICHD	1,318	90,600	935	49,216	70.9	54.3	991	70,951	453	34,212	45.7	48.2
NEI	632	40,205	538	26,564	85.1	66.1	542	36,143	350	24,422	64.6	67.6
NIEHS	397	25,820	262	13,535	66.0	52.4	263	18,721	119	9,083	45.2	48.5
NIA	425	27,867	249	11,652	58.6	41.8	249	16,243	85	7,185	34.1	44.2

NOTE: In prior NIH submissions, the total eligible for funding included council recommended for approval plus carryovers from the prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available , the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1979
(DOLLARS IN THOUSANDS)

INSTITUTE	DIRECT COSTS ONLY						TOTAL COSTS					
	REPORTING YEAR APPLICATIONS				COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	REVIEWED		COUNCIL RECOMMENDED*									
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
	14,461	$1,132,517	11,207	$660,790	77.5	58.3	11,510	$924,530	5,944	$525,473	51.6	56.8
NCI	2,569	241,099	2,047	141,505	79.7	58.7	2,051	196,288	901	109,549	43.9	55.8
NHLBI	2,239	191,979	1,679	106,179	75.0	55.3	1,699	146,151	942	88,790	55.4	60.8
NIDR	388	23,993	228	10,502	58.8	43.8	288	18,398	131	8,091	45.5	44.0
NIADDKD	1,822	131,682	1,494	80,837	82.0	61.4	1,539	113,440	769	62,975	50.0	55.5
NINCDS	1,236	107,402	921	57,869	74.5	53.9	922	78,584	577	46,232	62.6	58.8
NIAID	1,238	85,136	1,104	59,791	89.2	70.2	1,104	81,467	537	42,951	48.6	52.7
NIGMS	1,860	133,305	1,627	85,561	87.5	64.2	1,754	123,426	1,020	76,219	58.2	61.8
NICHD	1,524	110,323	1,011	58,782	66.3	53.3	1,028	81,898	461	40,918	44.8	50.0
NEI	527	37,449	456	25,749	86.5	68.8	462	36,367	301	25,117	65.2	69.1
NIEHS	327	21,874	220	12,850	67.3	58.7	222	18,131	91	8,907	41.0	49.1
NIA	731	48,275	420	21,165	57.5	43.8	441	30,381	214	15,724	48.5	51.8

NOTE: In prior NIH submissions, the total eligible for funding included council recommended for approval plus carryovers from the prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1980
(DOLLARS IN THOUSANDS)

INSTITUTE	DIRECT COSTS ONLY						TOTAL COSTS					
	REPORTING YEAR APPLICATIONS				COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	REVIEWED		COUNCIL RECOMMENDED*									
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
	14,142	$1,146,196	11,220	$695,726	79.3	60.7	11,301	$961,547	4,785	$472,484	42.3	49.1
NCI	2,523	244,237	1,975	138,528	78.3	56.7	1,982	192,336	773	92,281	39.0	48.0
NHLBI	2,190	186,739	1,735	114,423	79.2	61.3	1,741	155,449	589	66,478	33.8	42.8
NIDR	329	21,441	216	11,286	65.7	52.6	257	18,863	97	7,600	37.7	40.3
NIADDKD	1,966	146,336	1,628	92,662	82.8	63.3	1,631	126,511	698	61,023	42.8	48.2
NINCDS	1,262	105,855	950	61,232	75.3	57.8	951	82,465	503	51,581	52.9	62.5
NIAID	1,313	97,999	1,179	69,332	89.8	70.7	1,181	96,527	452	39,130	38.3	40.5
NIGMS	1,695	122,334	1,511	85,147	89.1	69.6	1,527	119,166	890	78,563	58.3	65.9
NICHD	1,413	110,481	957	58,948	67.7	53.4	958	81,546	348	32,613	36.3	40.0
NEI	494	36,950	415	24,572	84.0	66.7	416	33,843	217	20,020	52.2	59.2
NIEHS	316	24,142	248	15,038	78.5	62.3	248	21,069	87	8,529	35.1	40.5
NIA	641	49,681	406	24,560	63.3	49.4	409	33,772	131	14,666	32.0	43.4

NOTE: In prior NIH submissions, the total eligible for funding included council recommended for approval plus carryovers from the prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1981
(DOLLARS IN THOUSANDS)

- A C T U A L -

INSTITUTE	DIRECT COSTS ONLY						TOTAL COSTS					
	REPORTING YEAR APPLICATIONS				COUNCIL RECOMMENDED RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	REVIEWED		COUNCIL RECOMMENDED*									
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
	15,731	$1,368,080	12,939	$888,569	82.3	65.0	13,027	$1,240,975	5,109	$545,036	39.2	$43.9
NCI.........	2,731	294,252	2,275	184,761	83.3	62.8	2,276	257,553	814	101,246	35.8	39.3
NHLBI.......	2,289	208,042	1,890	135,193	82.6	65.0	1,897	187,137	774	86,484	40.7	46.2
NIDR........	380	27,565	271	17,103	71.3	62.0	317	27,344	143	13,047	45.1	47.7
NIADDK......	2,155	176,372	1,840	118,113	85.4	67.0	1,853	163,713	759	74,354	41.0	45.4
NINCDS......	1,547	130,350	1,198	80,414	77.4	61.7	1,198	110,623	487	51,820	40.6	46.8
NIAID.......	1,374	102,528	1,242	76,867	90.4	75.0	1,242	108,959	433	44,713	34.9	41.0
NIGMS.......	1,958	160,733	1,769	115,425	90.3	71.8	1,771	160,877	711	74,752	40.1	46.5
NICHD	1,590	128,413	1,148	76,205	72.2	59.3	1,156	106,876	453	44,897	39.2	42.0
NEI.........	643	50,792	580	37,154	90.2	73.1	580	50,973	304	28,890	52.4	56.7
NIEHS.......	300	25,393	229	15,831	76.3	62.3	238	22,632	113	11,568	47.5	51.1
NIA.........	764	63,640	497	31,503	65.1	49.5	499	44,288	118	13,265	23.6	30.0

NOTE: In prior NIH submissions, the total eligible for funding includes council recommended for approval plus carryovers from the prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, (1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and (2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1982
(DOLLARS IN THOUSANDS)

- A C T U A L -

INSTITUTE	---DIRECT COSTS ONLY---						***TOTAL COSTS***					
	REPORTING YEAR APPLICATIONS				COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		F U N D E D		AWARD RATE	
	R E V I E W E D		COUNCIL RECOMMENDED*									
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
	16,989	$1,598,512	14,396	$1,081,263	84.7	67.6	14,479	$1,529,076	5,027	$564,620	34.7	$36.9
NCI........	2,910	332,809	2,500	217,438	85.9	65.3	2,502	309,509	748	96,775	29.9	31.3
NHLBI......	2,455	247,986	2,054	169,529	93.7	68.4	2,055	238,025	765	99,733	37.2	41.9
NIDR.......	386	29,174	258	16,539	66.8	56.7	275	24,308	108	10,402	39.3	42.8
NIADDK.....	2,289	203,323	1,985	140,411	86.7	69.1	1,985	193,654	645	68,300	32.5	35.3
NINCDS.....	1,717	154,044	1,431	100,409	83.3	65.2	1,433	138,639	500	52,921	34.9	38.2
NIAID......	1,550	124,524	1,437	96,449	92.7	77.5	1,437	134,865	411	43,918	28.6	32.6
NIGMS......	2,330	207,353	2,159	152,895	92.7	73.7	2,206	211,153	859	90,834	38.9	43.0
NICHD......	1,559	132,481	1,254	86,736	78.4	65.5	1,254	122,403	439	44,194	35.0	36.1
NEI........	643	54,244	561	40,409	87.2	74.5	564	56,592	273	26,910	48.4	47.6
NIEHS......	411	37,140	274	20,880	66.7	56.2	274	29,457	104	10,927	38.0	37.1
NIA........	699	75,434	483	39,568	69.1	52.5	494	62,899	175	19,706	35.4	31.3

NOTE: In prior NIH submissions, the total eligible for funding includes council recommended for approval plus carryovers from the prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, (1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and (2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1983
(DOLLARS IN THOUSANDS)

- A C T U A L -

INSTITUTE	--------DIRECT COSTS ONLY--------						********TOTAL COSTS********					
	REPORTING YEAR APPLICATIONS				COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		F U N D E D		AWARD RATE	
	R E V I E W E D		COUNCIL RECOMMENDED*									
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
	16798	$1,618,401	14425	$1,137,912	85.9	$70.3	14482	$1,621,162	5389	$643,396	37.2	$39.7
NCI........	3042	342,512	2606	232,747	85.7	67.9	2610	332,725	886	111,896	33.9	33.6
NHLBI......	2519	266,295	2110	186,143	83.8	69.9	2114	263,259	748	116,989	35.4	44.4
NIDR.......	333	28,134	226	15,791	67.9	56.1	252	24,760	133	13,505	52.8	54.5
NIADDK.....	2210	200,261	1993	148,148	90.2	73.9	2000	209,531	777	87,331	38.9	41.7
NINCDS.....	1785	152,246	1514	104,900	84.8	68.9	1522	150,325	539	53,479	35.4	35.6
NIAID......	1519	140,653	1406	107,278	92.6	76.3	1406	155,515	522	59,910	37.1	38.5
NIGMS......	2188	195,185	2035	148,696	93.0	76.2	2040	209,226	835	92,760	40.9	44.3
NICHD......	1607	135,095	1302	91,524	81.0	67.8	1302	130,069	452	45,852	34.7	35.3
NEI........	597	48,140	549	38,392	91.9	79.8	552	55,466	247	25,930	44.7	46.7
NIEHS.......	277	29,962	210	20,615	75.8	68.8	210	29,281	98	14,717	46.7	50.3
NIA	721	79,918	474	43,678	65.7	54.7	474	61,005	152	21,027	32.1	34.5

NOTE: In prior NIH submissions, the total eligible for funding includes council recommended for approval plus carryovers from the prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in wl carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, (1) in all years for which actual data is available, the total eligible for funding includes the council recommended for appro plus funded carryover from the prior year; and (2) for the current year and budget year estimates, the total eligible for funding incl only those applications recommended for approval by council.

TIONAL INSTITUTES OF HEALTH
RESEARCH ECT APPLICATIONS REVIEWED & FUNDED, 1984
(DOLLARS IN THOUSANDS)

-ACTUAL-

	DIRECT COSTS ONLY						TOTAL COSTS					
	REPORTING YEAR APPLICATIONS REVIEWED		COUNCIL RECOMMENDED		COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
NCI	3029	354,334	2,518	232,594	83.1	65.3	2,534	346,450	969	157,635	38.2	45.5
NHLBI	2445	263,877	2,115	183,601	86.5	69.6	2,119	262,900	852	119,808	40.2	45.6
NIDR	372	30,408	283	19,973	76.1	65.5	283	28,786	123	13,438	43.5	46.7
NIADDK	2247	217,378	2,020	160,644	89.9	73.9	2,024	228,882	785	96,542	38.8	42.2
NINCDS	1908	176,279	1,629	127,067	85.4	72.1	1,634	180,337	564	70,907	34.5	39.3
NIAID	1498	137,871	1,398	107,154	93.3	77.7	1,408	156,928	507	61,252	36.0	39.0
NIGMS	2113	198,850	1,953	152,666	92.4	76.8	1,955	217,693	702	89,322	35.9	41.0
NICHD	1661	149,134	1,405	110,221	84.6	73.9	1,422	160,323	415	51,835	29.2	32.3
NEI	660	58,657	613	46,076	92.9	78.6	620	68,288	309	35,387	49.8	51.8
NIEHS	323	32,028	279	24,083	86.4	75.2	280	34,334	138	16,481	49.3	48.0
NIA	645	70,480	459	42,960	71.2	61.0	459	60,691	129	19,309	28.1	31.8
TOTAL,NIH	16,901	1,691,376	14,672	1,207,039	86.8	71.4	14,738	1,745,612	5,493	731,916	37.3	41.9

NOTE: In prior NIH submissions, the total eligible for funding included council recommended for approval plus carryovers from prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

INCLUDES SBIR APPROVED/RECOMMENDED/OR FUNDED

NATIONAL ,TUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, 1985
(DOLLARS IN THOUSANDS)

-ACTUAL-

	DIRECT COSTS ONLY						TOTAL COSTS					
	REVIEWED		COUNCIL RECOMMENDED		COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
NCI	3183	$396,209	2788	$289,897	87.6%	73.2%	2791	$423,565	1017	$168,464	36.4%	39.8%
NHLBI	2778	342,953	2441	254,730	87.9	74.3	2448	361,903	901	158,203	36.8	43.7
NIDR	381	33,818	317	25,771	83.2	76.2	318	36,586	131	15,859	41.2	43.3
NIADDK	2462	247, 46	2237	186,570	90.9	75.5	2240	267,956	786	104,756	35.1	39.1
NINCDS	2127	261,436	1903	193,758	89.5	74.1	1908	275,725	722	105,978	37.8	38.4
NIAID	1635	159,704	1504	121,960	92	76.4	1504	178,299	549	72,045	36.5	40.4
NIGMS	2299	232,976	2165	184,622	94.2	79.2	2202	268,600	987	133,845	44.8	49.8
NICHD	1880	179,839	1647	137,204	87.6	76.3	1662	200,438	469	64,200	28.2	32
NEI	788	76,202	737	59,914	93.5	78.6	746	87,686	367	47,230	49.2	53.9
NIEHS	389	41,600	334	31,409	85.9	75.5	334	45,373	108	16,624	32.3	36.6
NIA	752	84,258	588	58,176	78.2	69	609	87,304	209	30,895	34.3	35.4
TOTAL,NIH	18674	2,056,141	16661	1,544,011	89.2	75.1	16762	2,233,435	6,246	918,099	37.3	41.1

NOTE: In prior NIH submissions, the total eligible for funding included council recommended for approval plus carryovers from prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

Includes SBIR approved, recommended or funded.

NATIONAL ITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, 1986
(DOLLARS IN THOUSANDS)

-ESTIMATE-

	DIRECT COSTS ONLY						TOTAL COSTS					
	REVIEWED		COUNCIL RECOMMENDED		COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
NCI	3497	$455,361	3111	$351,616	89.0%	77.2%	3111	$530,846	857	$161,512	27.5%	30.4%
NHLBI	2801	356,762	2523	266,538	90.1	74.7	2523	392,117	817	143,954	32.4	36.7
NIDR	422	41,342	348	30,812	82.5	74.5	348	44,586	149	17,309	42.8	38.8
NIDDK	1921	210,819	1821	167,123	94.8	79.3	1821	241,159	564	86,756	31	36
NINCDS	2390	294,288	2238	230,361	93.6	78.3	2238	337,673	598	91,083	26.7	27
NIAID	1717	186,900	1616	146,684	94.1	78.5	1616	216,700	465	70,770	28.8	32.7
NIGMS	2458	257,409	2335	207,434	95	80.6	2335	300,215	810	124,359	34.7	41.4
NICHD	1920	189,377	1764	153,259	91.9	80.9	1764	225,175	467	64,379	26.5	28.6
NEI	690	68,647	657	56,527	95.2	82.3	657	85,849	331	41,856	50.4	48.8
NIEHS	407	42,958	363	35,074	89.2	81.6	363	49,741	111	16,203	30.6	32.6
NIA	760	90,152	582	64,147	76.6	71.2	582	90,444	177	28,425	30.4	31.4
NIAMSD	663	72,733	628	57,658	94.7	79.3	628	83,200	173	24,606	27.5	29.6
TOTAL,NIH	19646	2,266,748	17986	1,767,233	91.6	78	17986	2,597,705	5519	871,212	30.7	33.5

NOTE: In prior NIH submissions, the total eligible for funding included council recommended for approval plus carryovers from prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

Includes SBIR approved, recommended or funded.

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, 1986
(DOLLARS IN THOUSANDS)

APPROPRIATION AFTER SEQUESTRATION

	DIRECT COSTS ONLY						TOTAL COSTS					
	REVIEWED		COUNCIL RECOMMENDED		COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
NCI	3497	$455,361	3111	$351,616	89.0%	77.2%	3111	$530,846	931	$168,312	29.9%	31.7%
NHLBI	2801	356,762	2523	266,538	90.1	74.7	2523	392,117	886	155,423	35.1	39.6
NIDR	422	41,342	348	30,812	82.5	74.5	348	44,586	149	17,309	42.8	38.8
NIADDK	1921	210,819	1821	167,123	94.8	79.3	1821	241,159	637	93,212	35.0	38.7
NINCDS	2390	294,288	2238	230,361	93.6	78.3	2238	337,673	646	100,637	28.9	29.8
NIAID	1717	186,900	1616	146,684	94.1	78.5	1616	216,700	527	73,874	32.6	34.1
NIGMS	2458	257,409	2335	207,434	95.0	80.6	2335	300,215	972	132,874	41.6	44.3
NICHD	1920	189,377	1764	153,259	91.9	80.9	1764	225,175	483	64,779	27.4	28.8
NEI	690	68,647	657	56,527	95.2	82.3	657	85,849	358	45,046	54.5	52.5
NIEHS	407	42,958	363	35,074	89.2	81.6	363	49,741	111	16,203	30.6	32.6
NIA	760	90,152	582	64,147	76.6	71.2	582	90,444	201	31,104	34.5	34.4
NIAMSD	663	72,733	628	57,658	94.7	79.3	628	83,200	199	26,130	31.7	31.4
TOTAL,NIH	19646	2,266,748	17986	1,767,233	91.6	78.0	17986	2,597,705	6100	924,903	33.9	35.6

NOTE: In prior NIH submissions, the total eligible for funding included council recommended for approval plus carryovers from prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

Includes SBIR approved, recommended or funded.

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, 1986
(DOLLARS IN THOUSANDS)

APPROPRIATION

	DIRECT COSTS ONLY						TOTAL COSTS					
	REVIEWED		COUNCIL RECOMMENDED		COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
NCI	3497	$455,361	3111	$351,616	89.0%	77.2%	3111	$530,846	931	$175,707	29.9%	33.1%
NHLBI	2801	356,762	2523	266,538	90.1	74.7	2523	392,117	886	162,378	35.1	41.4
NIDR	422	41,342	348	30,812	82.5	74.5	348	44,386	149	18,083	42.8	40.6
NIDDK	1921	210,819	1821	167,123	94.8	79.3	1821	241,159	637	96,949	35.0	40.2
NINCDS	2390	294,288	2238	230,361	93.6	78.3	2238	337,673	646	105,159	28.9	31.1
NIAID	1717	186,900	1616	146,684	94.1	78.5	1616	216,700	527	77,168	32.6	35.6
NIGMS	2458	257,409	2335	207,434	95.0	80.6	2335	300,215	972	138,792	41.6	46.2
NICHD	1920	189,377	1764	153,259	91.9	80.9	1764	225,175	483	67,668	27.4	30.1
NEI	690	68,647	657	56,527	95.2	82.3	657	85,849	358	47,066	54.5	54.8
NIEHS	407	42,958	363	35,074	89.2	81.6	363	49,741	111	16,931	30.6	34.0
NIA	760	90,152	582	64,147	76.6	71.2	582	90,444	201	32,442	34.5	35.9
NIAMSD	663	72,733	628	57,658	94.7	79.3	628	83,200	199	27,611	31.7	33.2
TOTAL,NIH	19646	2,266,748	17986	1,767,233	91.6	78.0	17986	2,597,705	6100	965,954	33.9	37.2

NOTE: In prior NIH submissions, the total eligible for funding included council recommended for approval plus carryovers from prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

Includes SBIR approved, recommended or funded.

NATIONAL ,TUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, 1987
(DOLLARS IN THOUSANDS)

-ESTIMATE-

	DIRECT COSTS ONLY						TOTAL COSTS					
	REVIEWED		COUNCIL RECOMMENDED		COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
NCI	3663	$505,631	3267	$388,205	89.2%	76.8%	3267	$595,068	874	$149,070	26.8%	25.1%
NHLBI	2915	393,672	2685	302,539	92.1	76.9	2685	450,629	802	145,635	29.9	32.3
NIDR	416	43,471	352	33,761	84.6	77.7	352	49,010	110	12,683	31.3	25.9
NIDDK	1969	225,000	1895	181,354	96.2	80.6	1895	263,508	566	82,627	29.9	31.4
NINCDS	2479	323,730	2389	262,705	96.4	81.1	2389	390,390	538	80,126	22.5	20.5
NIAID	1668	185,578	1576	145,525	94.5	78.4	1576	216,917	421	58,126	26.7	26.8
NIGMS	2335	251,926	2246	207,520	96.2	82.4	2246	302,326	689	100,867	30.7	33.4
NICHD	1928	195,618	1851	167,132	96	85.4	1851	248,162	456	62,826	24.6	25.3
NEI	721	75,784	699	63,660	96.9	84	699	98,520	250	33,869	35.8	34.4
NIEHS	450	51,379	417	42,640	92.7	83	417	60,855	105	15,301	25.2	25.1
NIA	730	90,529	579	68,632	79.3	75.8	579	97,032	145	23,502	25	24.2
NIAMSD	679	77,626	654	62,568	96.3	80.6	654	90,911	148	19,909	22.6	21.9
TOTAL, NIH	19953	2,419,944	18610	1,926,241	93.3	79.6	18610	2,863,328	5104	784,541	27.4	27.4

NOTE: In prior NIH submissions, the total eligible for funding included council recommended for approval plus carryovers from prior year that were eligible and considered for funding in the subsequent year. A policy decision has recently been made to change the way in which carryover is reported to ensure a greater degree of uniformity in data presentation among the NIH awarding units. As a result of this change, 1) in all years for which actual data is available, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year; and 2) for the current year and budget year estimates, the total eligible for funding includes only those applications recommended for approval by council.

Includes SBIR approved, recommended or funded.

DHHS - National Institutes of Health
1985 COLUMN OF 1987 CONGRESSIONAL

(In thousands)

Research Grants	NCI		NHLBI		NIDR		NIADDK		NINCDS		NIAID		NIGMS		NICHD		NEI		NIEHS		NIA		DRR		FIC		TOTAL	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:																												
Noncompeting	1907	$332,083	1732	$318,133	266	$31,198	1814	$259,765	1144	$148,144	1128	$166,627	1907	$259,990	898	$119,672	701	$84,646	234	$35,565	269	$49,787					12000	$1,805,610
Admin. supp.	(160)	7,747	(38)	1,226	(1)	70	(92)	7,847	(36)	3,412	(10)	667	(75)	2,990	(78)	3,732	(49)	1,348	(7)	443	(26)	989					(500)	30,479
Competing	999	167,633	901	158,203	131	15,859	786	104,756	722	105,978	540	70,728	987	133,845	469	64,200	367	47,230	108	16,624	209	30,895					6219	915,951
Subtot., C	999	167,633	901	158,203	131	15,859	786	104,756	722	105,978	540	70,728	987	133,845	469	64,200	367	47,230	108	16,624	209	30,895					6219	915,951
Subtot.,RPG	2906	507,463	2633	477,562	397	47,127	2600	372,368	1866	257,534	1668	238,022	2894	396,833	1367	187,604	1068	133,224	342	52,632	478	81,671					18219	2,752,040
Research Ctrs:																												
Spec/comp.	58	84,957	60	84,112	13	13,000	45	35,011	40	30,133	18	5,590	15	9,235	43	27,559	28	5,765	15	15,101	12	9,513					347	319,976
GCRC																							78	$86,805			78	86,805
Biotech																							61	34,962			61	34,962
LASPR																							46	28,869			46	28,869
Gorgas																									1	$1,999	1	1,999
Subtotal	58	84,957	60	84,112	13	13,000	45	35,011	40	30,133	18	5,590	15	9,235	43	27,559	28	5,765	15	15,101	12	9,513	185	150,636	1	1,999	533	472,611
Other Res.:																												
Careers	127	6,799	356	22,101	47	2,907	246	15,370	204	10,993	78	4,058	16	609	113	5,962	18	1,001	24	1,340	79	4,813	6	324			1314	76,277
Organ sys.	1	935																									1	935
Clin. ed.	45	3,963																									45	3,963
Coop. cl.	271	50,822	16	1,796																							287	52,618
BRS																							720	95,733			720	95,733
MPRS		3,373		2,399		92		1,629		177		414				516		308		509		226	95	24,612			95	34,255
Other	58	3,679	74	10,428	76	1,335	39	2,375	30	1,944	30	743	28	2,334	21	1,044	35	1,211	12	439	63	1,896	89	16,865			555	44,293
Subtotal	502	69,571	446	36,724	123	4,334	285	19,374	234	13,114	108	5,215	44	2,943	134	7,522	53	2,520	36	2,288	142	6,935	918	137,534			3025	308,074
Total,RGs	3466	661,991	3139	598,398	533	64,461	2930	426,753	2140	300,781	1794	248,827	2953	409,011	1544	222,685	1149	141,509	393	70,021	632	98,119	1103	288,170	1	1,999	21777	3,532,725
Training																												
Indiv.	241	5,308	210	5,191	37	974	203	4,994	253	5,486	75	1,849	502	10,668	127	2,904	111	2,465	44	784	24	553	4	91			1831	41,267
Instit.	1223	25,489	1499	34,432	160	3,829	843	21,711	370	7,664	442	9,440	2894	47,053	575	10,958	109	2,766	439	7,718	203	4,058	35	984			8792	176,102
Total	1464	30,797	1709	39,623	197	4,803	1046	26,705	623	13,150	517	11,289	3396	57,721	702	13,862	220	5,231	483	8,502	227	4,611	39	1,075			10623	217,369
Contracts	415	143,142	214	56,737	21	4,696	31	9,885	76	14,163	74	18,672	5	1,234	114	23,040	42	7,123	177	35,611		11,557	3	5,103			1172	350,963
Intramural		197,838		61,487		19,864		57,215		48,123		51,142		784		35,862		15,466		53,459		20,440						561,600
RM&S		59,639		35,482		6,796		15,530		17,761		14,407		12,874		14,374		5,382		6,130		8,582		8,291		9,515		214,763
Control		63,794																										63,794
Construct.		6,500		3,300														3,300										13,100
Total, IRDs		1,163,701		795,027		100,620		536,088		393,978		344,337		481,624		307,823		178,011		193,723		143,309		302,639		11,514		4,954,394

National Library of Medicine	54,098
Office of the Director	34,179
Buildings and Facilities	15,675
Total, NIH	5,058,346

DHHS - National Institutes of Health
1986 APPROPRIATION

(In thousands)

Research Grants	NCI No.	NCI Amount	NHLBI No.	NHLBI Amount	NIDR No.	NIDR Amount	NIADDK No.	NIADDK Amount	NINCDS No.	NINCDS Amount	NIAID No.	NIAID Amount	NIGMS No.	NIGMS Amount	NICHD No.	NICHD Amount	NEI No.	NEI Amount	NIEHS No.	NIEHS Amount	NIA No.	NIA Amount	DRR No.	DRR Amount	FIC No.	FIC Amount	TOTAL No.	TOTAL Amount
Research Proj.:																												
Noncompeting	2090	$399,538	1818	$369,412	248	$28,926	1790	$274,269	1273	$188,114	1162	$174,615	1971	$290,228	891	$130,271	783	$101,469	247	$39,173	303	$60,130					12576	$2,056,145
Admin. supp.	(152)	6,575	(35)	1,162			(79)	4,713	(33)	1,000	(16)	573	(17)	675	(40)	1,272	(45)	880	(10)	528	(8)	128					(435)	17,506
Competing	924	175,325	886	162,378	149	18,083	836	124,560	645	104,986	508	73,618	972	138,792	483	67,668	358	47,066	111	16,931	201	32,442					6073	961,849
Subtot., C	924	175,325	886	162,378	149	18,083	836	124,560	645	104,986	508	73,618	972	138,792	483	67,668	358	47,066	111	16,931	201	32,442					6073	961,849
Subtot., RPG	3014	581,438	2704	532,952	397	47,009	2626	403,542	1918	294,100	1670	248,806	2943	429,695	1374	199,211	1141	149,415	358	56,632	504	92,700					18649	3,035,500
Research Ctrs:																												
Spec/comp.	58	85,823	60	86,535	16	13,905	45	35,598	38	30,150	18	5,809	16	10,219	43	27,538	29	6,100	15	15,391	12	10,396					350	327,464
GCRC																							78	$89,896			78	89,896
Biotech																							61	35,632			61	35,632
LASFR																							46	30,346			46	30,346
Gorgas																									1	$1,999	1	1,999
Subtotal	58	85,823	60	86,535	16	13,905	45	35,598	38	30,150	18	5,809	16	10,219	43	27,538	29	6,100	15	15,391	12	10,396	185	155,874	1	1,999	536	485,337
Other Res.:																												
Careers	122	6,907	364	22,915	58	4,204	223	15,021	226	12,405	71	3,979	16	611	110	6,059	15	887	28	1,484	71	4,759	6	346			1310	79,577
Organ sys.	1	1,000																									1	1,000
Clin. ed.	52	4,700																									52	4,700
Coop. cl.	255	50,204	16	1,142					1	1,000																	272	52,346
BRS																							720	95,500			720	95,500
MBRS		3,400		2,500		117		1,600		200		460				589		315		371		373	92	24,951			92	34,876
Other	34	3,440	55	9,159	75	1,311	36	2,642	21	$1,871	11	877	21	$2,017	8	962	35	1,176	6	$423	14	1,079	76	12,487	155	4,622	547	42,066
Subtotal	464	69,651	435	35,716	133	5,632	259	19,263	248	15,476	82	5,316	37	2,628	118	7,610	50	2,378	34	2,278	85	6,211	894	133,284	155	4,622	2994	310,065
Total, RGs	3536	736,912	3199	655,203	546	66,546	2930	458,403	2204	339,726	1770	259,931	2996	442,542	1535	234,359	1220	157,893	407	74,301	601	109,307	1079	289,158	156	6,621	22179	3,830,902
Training																												
Individual	204	4,626	234	6,031	50	1,250	158	3,905	208	4,501	85	2,156	345	7,678	103	2,550	108	2,615	38	710	33	782	3	84			1569	36,888
Institutional	1082	26,212	1476	34,175	162	3,312	1012	22,825	417	8,652	406	9,097	2894	50,043	571	11,351	100	2,616	439	7,792	207	4,725	36	991			8802	181,791
Total	1286	30,838	1710	40,206	212	4,562	1170	26,730	625	13,153	491	11,253	3239	57,721	674	13,901	208	5,231	477	8,502	240	5,507	39	1,075			10371	218,679
Contracts	451	139,706	189	53,080	35	4,686	40	$11,850	67	13,102	59	18,134	5	1,263	109	23,152	48	6,649	178	54,443	48	13,733	6	5,189			1235	344,987
Intramural		$194,102		$60,764		$19,996		58,758		$48,615		51,350		875		$35,518		16,051		54,130		$20,885						561,044
RM&S		59,484		35456		6,803		16,196		16,998		16,049		13,298		15,137		5,847		6,003		8,243		$8,400		$4,769		212,683
Control		63,878																										63,878
Construct.		2,000		3,300														3,300										8,600
Total, IRD		1,226,920		848,009		102,593		571,937		431,594		356,717		515,699		322,067		194,971		197,379		157,675		303,822		11,390		5,240,773

National Library of Medicine	57,759
Office of the Director	46,990
Buildings and Facilities	14,900
Total, NIH	5,360,422

DHHS - N 'nstitutes of Health
1986 ADJUSTEE ATION WITH SEQUESTRATION

(housands)

	NCI		NHLBI		NIDR		NIADDK		NINCDS		NIAID		NIGMS		NICHD		NEI		NIEHS		NIA		DRR		FIC		TOTAL	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:																												
Noncompeting	2090	$382,336	1818	$353,528	248	$27,682	1790	$262,475	1273	$180,025	1162	$167,106	1971	$277,748	891	$124,669	783	$97,106	247	$37,489	303	$57,544					12576	1,967,708
Admin. supp.	(152)	6,292	(35)	1,112			(79)	4,510	(33)	957	(16)	548	(17)	646	(40)	1,217	(45)	842	(10)	505	(8)	123					(435)	16,752
Competing	924	167,955	886	155,423	149	17,309	836	119,342	645	$100,464	508	70,477	972	132,874	483	64,779	358	45,046	111	16,203	201	31,104					6073	920,976
Subtot., C	924	167,955	886	155,423	149	17,309	836	119,342	645	100,464	508	70,477	972	132,874	483	64,779	358	45,046	111	16,203	201	31,104					6073	920,976
Subtot.,RPG	3014	556,583	2704	510,063	397	44,991	2626	386,327	1918	281,446	1670	238,131	2943	411,268	1374	190,665	1141	142,994	358	54,197	504	88,771					18649	2,905,436
Research Ctrs:																												
Spec/comp.	57	82,132	60	82,814	16	13,307	45	34,067	38	28,853	18	5,559	15	9,780	43	26,355	29	5,838	15	14,729	12	9,949					348	313,383
GCRC																							78	$86,031			78	86,031
Biotech																							61	34,100			61	34,100
LASPR																							46	29,041			46	29,041
Gorgas																									1	1,913	1	1,913
Subtotal	57	82,132	60	82,814	16	13,307	45	34,067	38	28,853	18	5,559	15	9,780	43	26,355	29	5,838	15	14,729	12	9,949	185	149,172	1	1,913	534	464,468
Other Res.:																												
Careers	117	6,610	364	21,930	55	4,023	212	14,375	216	11,872	68	3,809	15	585	105	5,798	15	849	27	1,420	70	4,554	6	331			1270	76,156
Organ sys.	1	957																									1	957
Clin. ed.	52	4,498																									52	4,498
Coop. cl.	228	48,045	16	1,093					1	957																	245	50,095
BRS																							713	91,393			713	91,393
MBRS		3,254		2,392		112		1,531		191		440				564		301		355		357	92	23,878			92	33,375
Other	33	3,292	55	8,766	72	1,255	34	2,529	19	$1,786	11	839	17	$1,920	8	921	35	1,125	6	$404	11	1,033	76	11,950	153	4,423	530	40,243
Subtotal	431	66,656	435	34,181	127	5,390	246	18,435	236	14,806	79	5,088	32	2,505	113	7,283	50	2,275	33	2,179	81	5,944	887	127,552	153	4,423	2903	296,717
Total,RGs	3502	705,371	3199	627,058	540	63,688	2917	438,829	2192	325,105	1767	248,778	2990	423,553	1530	224,303	1220	151,107	406	71,105	597	104,664	1072	276,724	154	6,336	22086	3,666,621
Training																												
Individual	195	4,427	217	5,772	48	1,196	155	3,838	199	4,307	69	1,722	312	6,831	99	2,440	108	2,503	36	679	32	748	3	81			1473	34,544
Institutional	1036	25,085	1410	32,705	156	3,170	966	21,743	399	8,280	394	9,048	2796	48,408	546	10,863	100	2,504	439	7,457	198	4,522	34	948			8474	174,733
Total	1231	29,512	1627	38,477	204	4,366	1121	25,581	598	12,587	463	10,770	3108	55,239	645	13,303	208	5,007	475	8,136	230	5,270	37	1,029			9947	209,277
Contracts	438	133,732	189	50,797	33	4,484	39	$11,314	67	12,539	57	17,354	5	1,209	106	22,156	48	6,363	168	52,102	46	13,142	6	4,965			1202	330,157
Intramural		$185,704		$58,150		$19,135		56,231		46,532		49,133		837		$33,981		15,360		51,001		$19,986						536,050
RM&S		56,911		33,904		6,508		15,500		16,261		15,358		12,726		14,486		5,591		5,743		7,884		$8,034		$4,557		203,463
Control		61,131																										61,131
Construct.		1,914		3,158														3,158										8,230
Total, IRDs		1,174,275		811,544		98,181		547,455		413,024		341,393		493,564		308,229		186,586		188,087		150,946		290,752		10,893		5,015,729

National Library of Medicine	55,273
Office of the Director	44,969
Buildings and Facilities	14,259
Total, NIH	5,130,230

DHHS - National Institutes of Health
1986 COLUMN OF 1987 CONGRESSIONAL

(In thousands)

Research Grants	NCI No.	NCI Amount	NHLBI No.	NHLBI Amount	NIDR No.	NIDR Amount	NIADDK No.	NIADDK Amount	NINCDS No.	NINCDS Amount	NIAID No.	NIAID Amount	NIGMS No.	NIGMS Amount	NICHD No.	NICHD Amount	NEI No.	NEI Amount	NIEHS No.	NIEHS Amount	NIA No.	NIA Amount	DRR No.	DRR Amount	FIC No.	FIC Amount	TOTAL No.	TOTAL Amount
Research Proj.:																												
Noncompeting	2090	$382,336	1818	$353,528	248	$27,682	1790	$262,475	1273	$180,025	1162	$168,697	1971	$278,918	891	$123,919	783	$95,072	247	$37,489	303	$57,544					12576	$1,967,685
Admin. supp.	(152)	6,292	(35)	1,112			(79)	4,510	(33)	957	(16)	548	(17)	633	(40)	1,217	(45)	842	(10)	505	(8)	123					(435)	16,739
Competing	850	161,155	817	143,954	149	17,309	737	111,362	597	$90,910	446	67,373	810	124,359	467	64,379	331	41,856	111	16,203	177	28,425					5492	867,285
Subtot., C	850	161,155	817	143,954	149	17,309	737	111,362	597	90,910	446	67,373	810	124,359	467	64,379	331	41,856	111	16,203	177	28,425					5492	867,285
Subtot., RPG	2940	549,783	2635	498,594	397	44,991	2527	378,347	1870	271,892	1608	236,618	2781	403,910	1358	189,515	1114	137,770	358	54,197	480	86,092					10068	2,851,709
Research Ctrs:																												
Spec/coop.	57	82,132	60	82,814	16	13,307	45	34,067	38	28,853	18	5,559	15	9,780	43	26,355	29	5,838	15	14,729	12	9,949					348	313,383
GCRC																							78	$86,031			78	86,031
Biotech																							61	34,100			61	34,100
LASPR																							46	29,041			46	29,041
Gorgas																									1	$1,913	1	1,913
Subtotal	57	82,132	60	82,814	16	13,307	45	34,067	38	28,853	18	5,559	15	9,780	43	26,355	29	5,836	15	14,729	12	9,949	185	149,172	1	1,913	534	464,468
Other Res.:																												
Careers	117	6,610	364	21,930	55	4,023	212	14,375	216	11,872	68	3,809	15	585	105	5,798	15	849	27	1,420	70	4,554	6	331			1270	76,156
Organ sys.	1	957																									1	957
Clin. ed.	52	4,498																									52	4,498
Coop. cl.	228	48,045	16	1,093					1	957																	245	50,095
BRS																							713	91,393			713	91,393
MBRS		3,254		2,392		112		1,531		191		440				564		301		355		357	92	23,878			92	33,375
Other	33	3,292	55	8,766	72	1,255	34	2,529	19	$1,786	11	839	17	$1,920	8	921	35	1,125	6	$404	11	1,033	76	11,950	153	4,423	530	40,243
Subtotal	431	66,656	435	34,181	127	5,390	246	18,435	236	14,806	79	5,088	32	2,505	113	7,283	50	2,275	33	2,179	81	5,944	887	127,552	153	4,423	2903	296,717
Total, RGs	3478	698,571	3130	615,589	540	63,688	2818	430,849	2144	315,551	1705	247,265	2828	416,195	1514	223,153	1193	145,883	406	71,105	573	101,985	1072	276,724	154	6,336	21505	3,612,894
Training																												
Indiv.	195	4,427	217	5,772	48	1,196	155	3,838	199	4,307	69	1,722	312	6,831	99	2,440	108	2,503	36	679	32	748	3	81			1473	34,544
Instit.	1036	25,085	1410	32,705	156	3,170	966	21,743	399	8,280	394	9,048	2796	48,408	546	10,863	100	2,504	439	7,457	198	4,522	34	948			8474	174,733
Total	1231	29,512	1627	38,477	204	4,366	1121	25,581	598	12,587	463	10,770	3108	55,239	645	13,303	208	5,007	475	8,136	230	5,270	37	1,029			9947	209,277
Contracts	438	133,732	189	50,797	33	4,484	39	$11,314	67	12,539	57	17,354	5	1,209	106	22,156	48	6,363	168	52,102	46	13,142	6	4,965			1202	330,157
Intramural		$185,704		$58,150		$19,135		56,231		46,532		49,133		837		$33,981		15,360		51,801		$19,986						536,850
RM&S		56,911		33904		6,508		15,500		16,261		15,358		12,726		14,486		5,591		5,743		7,884		$8,034		$4,557		203,463
Control		61,131																										61,131
Construct.		1,914		3,158														3,158										8,230
Total, BIDs		1,167,475		800,075		98,181		539,475		403,470		339,880		486,206		307,079		181,362		188,887		148,267		290,752		10,893		4,962,002

National Library of Medicine	55,273
Office of the Director	35,829
Buildings and Facilities	14,259
Total, NIH	5,067,363

DHHS - National Institutes of Health
1987 CONGRESSIONAL JUSTIFICATION

(In thousands)

	NCI		NHLBI		NIDR		NIDDKD		NINCDS		NIAID		NIGMS		NICHD		NEI		NIEHS		NIA		NIAMSD		DRR		FIC		TOTAL	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:																														
Noncompeting	2050	$381,489	1803	$352,109	269	$30,561	1361	$207,080	1313	$188,941	1178	$171,293	2082	$292,509	913	$125,465	853	$101,642	229	$37,098	345	$60,618	389	$54,702					12785	$2,003,307
Admin. supp.	(152)	6,575	(35)	1,162	--	---	(46)	1,436	(23)	668	(16)	524	(17)	703	(40)	1,340	(38)	1,750	(10)	514	(8)	128	(14)	400					(399)	15,20
Competing	874	149,070	802	145,635	110	12,683	566	82,627	538	80,126	421	58,126	689	100,867	456	62,826	250	33,869	105	15,301	145	23,502	148	19,909					5104	784,541
Subtot., C	874	149,070	802	145,635	110	12,683	566	82,627	538	80,126	421	58,126	689	100,867	456	62,826	250	33,869	105	15,301	145	23,502	148	19,909					5104	784,541
Subtot., RPG	2924	537,134	2605	498,906	379	43,244	1927	291,143	1851	269,735	1599	229,943	2771	394,079	1369	189,631	1103	137,261	334	52,913	490	84,248	537	75,011					17889	2,803,248
Research Ctrs:																														
Spec/coop.	57	82,282	60	75,757	16	11,790	31	23,682	38	26,371	14	3,734	11	6,559	43	26,217	29	5,400	15	14,482	12	9,812	14	9,317					340	295,403
GCRC																									76	86,082			76	86,082
Biotech																									60	33,898			60	33,898
LASPR																									46	29,905			46	29,905
Gorgas																											1	$1,934	1	1,934
Subtotal	57	82,282	60	75,757	16	11,790	31	23,682	38	26,371	14	3,734	11	6,559	43	26,217	29	5,400	15	14,482	12	9,812	14	9,317	182	149,885	1	$1,934	523	447,222
Other Res.:																														
Careers	122	6,907	364	21,906	58	4,204	160	10,692	216	11,872	68	3,979	18	677	105	5,798	12	625	25	1,322	68	4,512	48	3,409	6	346			1270	76,249
Organ sys.	1	800																											1	800
Clin. ed.	39	2,400																											39	2,400
Coop. cl.	239	49,884	16	1,035					1	957																			256	51,876
BRS																									154	32,883			154	32,883
MBRS		3,400		2,267		117		1,196		191		460				564		301		355		307		335	92	24,149			92	33,642
Other	30	3,161	55	8,489	65	1,135	26	1,405	19	1,892	11	914	2	1,865	8	921	20	850	6	420	10	829	8	1,124	76	12,122	153	4,557	489	39,684
Subtotal	431	66,552	435	33,697	123	5,456	186	13,293	236	14,912	79	5,353	20	2,542	113	7,283	32	1,776	31	2,097	78	5,648	56	4,868	328	69,500	153	4,557	2301	237,534
Total, RGs	3412	685,968	3100	608,360	518	60,490	2144	328,118	2125	311,018	1692	239,030	2802	403,180	1525	223,131	1164	144,437	380	69,492	580	99,708	607	89,196	510	219,385	154	6,491	20713	3,488,004
Training																														
Indiv.	189	4,292	203	5,140	42	1,050	116	2,856	199	4,307	55	1,414	194	4,404	95	2,351	98	2,300	33	670	30	713	35	881	3	84			1292	30,63
Instit.	1004	24,318	1297	28,629	162	3,312	719	16,188	399	8,280	320	7,569	2603	48,432	539	10,749	92	2,388	409	7,336	165	4,396	222	4,986	35	991			7966	167,57
Total	1193	28,610	1500	33,769	204	4,362	835	19,044	598	12,587	375	8,983	2797	52,916	634	13,100	190	4,776	442	8,006	195	5,109	257	5,867	38	1,075			9258	198,204
Contracts	435	133,960	189	51,919	34	4,586	30	8,393	60	11,529	47	15,235	5	1,263	115	22,156	55	7,215	168	52,045	42	12,590	6	2,536	6	5,031			1192	328,45
Intramural		190,291		56,065		20,303		49,980		47,804		51,492		875		35,746		16,723		52,647		20,250		6,191						548,35
RM&S		58,129		35,584		6,741		13,436		16,413		15,811		13,299		14,986		6,050		5,805		8,172		2,953		8,701		4,014		210,89
Control		61,131																												61,13
Construct.		---		---														---												--
Total, IRDs		1,158,089		785,697		96,482		418,971		399,351		330,551		471,533		309,119		179,201		187,995		145,829		106,733		234,192		11,305		4,835,04

National Library of Medicine	56,40
Office of the Director	36,70
Buildings and Facilities	8,00
Total, NIH	4,936,15

TUESDAY, MARCH 11, 1986.

NATIONAL CANCER INSTITUTE

WITNESSES

DR. VINCENT T. DeVITA, JR., DIRECTOR
DR. THOMAS MALONE, DEPUTY DIRECTOR, NIH
DR. PETER J. FISCHINGER, DEPUTY DIRECTOR, NCI
PHILIP D. AMORUSO, EXECUTIVE OFFICER, NCI
JOHN P. HARTINGER, FINANCIAL MANAGER, NCI
DENNIS P. WILLIAMS, ACTING DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. NATCHER. At this time we take up the budget request for Fiscal Year 1987 for the National Cancer Institute. We have before the Committee Dr. Vincent T. DeVita, Jr., the Director of the National Cancer Institute.

Dr. DeVita, it is a pleasure to have you back before the Committee. You have been here before.

Dr. DEVITA. Yes, indeed.

Mr. NATCHER. You know we are going to bring you out a good bill.

Dr. DEVITA. Yes.

Mr. NATCHER. We told you that last year. We brought you out a good bill last year, Dr. DeVita. We are going to bring you out a good one this year.

Before you give us your statement, Dr. DeVita, tell us who you have with you there at the table, please.

Dr. DEVITA. Certainly. Let me start on the right side of the table. Mr. Dennis Williams, representing the Department; on his left, Dr. Thomas Malone, Deputy Director of the National Institutes of Health.

On my immediate right, Mr. Chairman, is Dr. Peter Fischinger, whom you have not seen before; he is the new Deputy Director of the National Cancer Institute, replacing Dr. Jane Henney who used to accompany me to these hearings. Dr. Fischinger is a noted viral oncologist in his own right and a very accomplished administrator, and I am delighted to have him.

On my left is Mr. John Hartinger, the Financial Manager for the Institute, and on his left is Mr. Philip Amoruso, the Associate Director for Administrative Management of the Institute.

Mr. NATCHER. Gentleman, we are glad to have all of you before the Committee, and, Dr. DeVita, we will be pleased to hear from you at this time.

Dr. DEVITA. Thank you, Mr. Chairman.

I would like to submit my full statement for the record, if I may, and excerpt a few comments before we go to questions.

[Statement follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Cancer Institute, National Cancer Program

A basic tenet of the cancer program is that the understanding of how a normal cell becomes malignant is a requirement for the ultimate successful prevention and treatment of cancer. A corollary to this tenet is less widely appreciated: it is possible to prevent and to treat diseases including cancer even before full knowledge is available. Now, based on new knowledge of cancer biology, major efforts are under way to prevent cancer; to reverse the cancer process by nudging a transformed cell back to normal; to employ the exquisite network of our immune system to defend against cancer; to refine treatment and destroy more selectively cancer cells; and to block metastasis--the ability of cancer cells to spread and kill. The investment in basic research made possible by the National Cancer Program has led us today to an unprecedented understanding of the cancer cell.

This year, another piece of the cancer puzzle fell into place. Humans, like other living organisms, live in a sea of environmental toxins, most produced naturally, that are used to preserve each living organism's ecological niche. A simple example of this is the production of antibiotics by organisms in the soil to control the population of competing bacteria. We as physicians exploit these chemicals to treat bacterial infections and some cancers. A new conceptual unity has emerged that now connects such distant events as drug resistance in advanced cancers with the same fundamental mechanism of cancer transformation itself. It is now apparent that a common set of genes controls enzyme systems that resist the carcinogenic effects of environmental toxins and help prevent cancer in animals and humans. The ultimate failure of this process is followed by the loss of control of the switches that regulate growth, leading to malignancy. However, we now know that cancer cells retain these defenses in some capacity and are able to resist the very chemicals used to treat them. We can use this information on a practical level since modification of these resistance genes could improve treatment with drugs with potentially startling simplicity.

Cancer cells are renegades. They exert lethal effects by growing out of control, but they appear to be immature, somewhat confused cells, aberrantly using the same genetic mechanisms established for normal growth and development. The new biology allowed researchers to tap into this genetic machinery at the heart of the cell and find minute, but critical, differences in genes of normal and cancer cells. They discovered oncogenes involved in transforming healthy cells to cancer. The counterparts of these genes, proto-oncogenes, are involved in normal growth and development. It has long been thought that cancer is a multistage process with intricate circuits and switches, working at different points of disease progression and at different times. Some substances serve as initiators that start but cannot finish the cancer-causing process without the help of promoters. Most promoters cannot work in cells that have not been initiated. With new technology, we can study the genetic switches which trip the cascade of events that control growth and development or lead to cancer. Although cancer is over 100 different diseases, we now feel certain they share some basic mechanisms that set off the disease and have already exploited some of these data at the clinical level.

Recent research in cancer etiology has focused on how promoters work, because interfering with promotion may yield results by preventing cancer in persons exposed to initiators and offers the best hope in our lifetime of reducing cancer incidence. Powerful evidence already exists that this approach works. For example, curtailing wide use in the 1970's of the "promoter" estrogen, used for menopausal symptoms, led to a dramatic, fast reduction in uterine cancer. Cigarette smoke contains both initiators and promoters, but the removal of the promoters' effect may be the key event in avoiding lung cancer. This year, NCI reported that the incidence of lung cancer in white men has decreased significantly for the first time in at least 50 years. This provides evidence that the exposure to chemical initiators in cigarette smoke does not irreversibly destine a person to develop cancer and that people can reduce their cancer risk by interrupting the carcinogenic process at its later stages by quitting smoking. This type of evidence is the basis for multiple prospective intervention trials in progress at NCI to test the hypothesis that cancer can be prevented. The time interval to reduce risk may not be long in human terms. For example, the interval from smoking cessation to a return to normal risk of cancer is about a decade for most smoking-related cancers in man.

To emphasize these points further, I would like briefly to highlight a few past accomplishments and some current plans in cancer biology, prevention, diagnosis, and treatment.

Basic Biology

The development of major new technology has allowed scientists to put knowledge to work. Some brilliant Nobel-prize-winning discoveries of the 1970's led to development of many techniques that are routinely used today by scientists to cut, splice and analyze genes in detail (known as recombinant DNA technology). With these tools, researchers are able to probe, isolate, sequence, and scrutinize pieces of DNA, decode nature's messages, and make constructs of genes artificially. A technique called "marching down the chromosome" is streamlining studies of the DNA sequences that flank oncogenes and contain control switches. Using synthetic DNA probes that stick to oncogenes, scientists isolate and use the ends of large DNA fragments to probe and isolate additional ends of DNA further along the chromosome. This way, control elements can quickly be identified, compared, and sequenced.

An oncogene may be activated by mutation caused by a chemical, a virus, radiation, or as a result of a chromosomal break that moves the oncogene to a new location. Here it might be placed next to a signal switch that is normally "on" to produce normal protein, but, in this case, keeps the oncogene "abnormally on." Evidence of the activated ras oncogene (which has a mutation) has been found in a number of common human cancers, including lung, colon, and bladder cancers, and the myc gene in a lymphoma. Five different oncogenes associated with leukemias and lymphomas have been identified with specific translocation of pieces of chromosomes.

A few years ago, our researchers focused on the discovery of oncogenes, then their control switches, and now this work has moved toward understanding the products made by oncogenes and molecularly characterizing tumors as the new pathology. This year, protein products of the erb-B and fms oncogenes were found to be defective receptors for growth factors (substances that stimulate cell growth). The study of oncogenes and their control is also moving from the laboratory dish to studies in live animals. It is now possible to make combinations of different oncogenes and flanking DNA sequences in the laboratory, then inject these "foreign" genes into fertilized mouse eggs and produce mice (transgenic mice) in which every cell contains the foreign genes. The use of transgenic mice is an invaluable tool to examine ways to interrupt oncogene function and prevent or reverse the malignant process.

At the clinical level, oncogenes influence the aggressiveness of cancer cells and their ability to spread and invade distant, vital organs, causing death. Activation of more than one oncogene, and the presence of many copies of a single oncogene (gene amplification) have been closely linked with this metastatic process in lung, colon, and breast cancer.

Last year, NCI made major contributions in many areas of AIDS research. These included advances in understanding the molecular biology of the AIDS virus, HTLV-III; understanding the natural history and transmission of AIDS; identifying potential new therapies for the disease; and developing a vaccine and an animal model for the disease.

Cancer Prevention and Control at the Practical Level

The multistep process of carcinogenesis led the NCI to investigate practical ways to prevent cancer by interfering at the clinical level with the late, "promotion" stages of the process, some of which may be under control of known oncogenes. Evidence suggests that dietary fat serves as a promoter of cancer, while fiber protects colon cells from the effects of carcinogens. A study called the Women's Health Study is under way to determine whether low-fat diets can reduce breast cancer incidence in women at high risk for the disease. Studies are also looking at how fiber works to reduce risk of cancer. Recent studies point to the inhibitory role of both phytic acid (present in grain fibers) and uronic acid (in vegetable fiber).

Already 450 agents, some of them micronutrients, have been identified as possible inhibitors of cancer; in-depth analysis has begun on 15 percent of them. Twenty-six human chemoprevention studies (adding selected micronutrients such as vitamins A, C, E, and beta-carotene to diet) continue in an effort to interfere with the promotion stages of the cancer-causing process. The NCI is funding 34 intervention studies--involving about 5 million people--to find ways to reduce smoking. Adolescents, minorities, and women are targeted.

Meantime, NCI's SEER (Surveillance, Epidemiology, and End Results) Program tracks the incidence, survival, and mortality rates of cancer in the United States. These data, recently reviewed in depth at a National Cancer Advisory Board seminar, clearly show that progress made in cancer treatment has had a significant impact on national cancer survival statistics. Today, 50 percent of patients with serious cancers are curable, but 50 percent are not. The NCI has launched a special initiative to address the problem of excess cancers and cancer deaths (avoidable mortality) among minority populations.

Cancer Diagnosis

Monoclonal antibodies, designed to "home in" on cancer cells, already are being used to diagnose tumors, such as lymphomas, leukemias, and colon cancer. Monoclonals help detect metastatic breast cancer cells in the body fluids of some patients, and may be useful in finding hidden metastases in some patients with colon cancer and melanoma.

On another front in diagnosis, scientists are improving the use of Magnetic Resonance Imaging (MRI) to attempt to distinguish cancer from benign tumors. MRI is proving useful for defining tumors in lung, liver, brain, and other organs.

Cancer Treatment

A major, achievable goal in cancer treatment will be to characterize oncogene products and develop new strategies to inhibit their production or action. There is already a startling and practical clinical example where selection of therapy based on patterns of oncogene expression has led to improved results. Such approaches are being explored in a variety of tumors.

Progress continues in refining surgery, radiotherapy, and chemotherapy as effective treatments for many cancer patients, and biological agents are rapidly adding to the therapeutic armamentarium. The NCI´s Biological Response Modifier Program, established in 1980, is playing a substantial role in bringing new agents to clinical trial. Using recombinant DNA technology, the genes of several body proteins, interferon, Interleukin-2 (IL-2), and tumor necrosis factor, have been prepared in large enough quantities to initiate clinical studies. This year, a very promising trial of biologicals was reported, using adoptive immunotherapy--the transfer of anticancer immune cells directly to the cancer patient. Early results in patients with advanced cancers who were treated by these IL-2 Activated Killer (LAK) cells and very high doses of IL-2 have been most encouraging, especially in cancers of the kidney, the colon, and melanoma. The NCI is now testing this treatment across the country in its network of cancer centers and cooperative clinical groups.

Chemotherapy is improving as well. During 1985, adjuvant chemotherapy used after surgery produced positive results in heretofore difficult-to-treat cancers such as breast, rectal, colon cancer, and adenocarcinoma of the lung. The resistance that certain cancer cells develop to drugs, alluded to early in this statement, has been a major obstacle to curing some common cancers with drugs. A surface marker associated with this drug resistance has been identified and an antibody to the marker reverses drug resistance in the laboratory. This will be tested in the clinic in the next year.

Recently, understanding the deadly process of metastasis has led to a new approach to block it. Cancer cells spread by adhering to a protein laminin, found on the lining of blood vessels. Small fragments of laminin have been prepared which can block the cancer cells' laminin receptor and so prevent attachment to laminin on the vessel's basement membrane. This novel treatment approach begins clinical trials this year.

Human cells from small cell lung cancers produce a growth factor known as bombesin, capable of stimulating the cancer's own growth. A monoclonal antibody against bombesin is now entering clinical trial.

Mr. Chairman, the Fiscal Year 1987 budget request for this Institute is $1,158,089,000. I will be happy to answer any questions.

CURRICULUM VITAE

NAME: Vincent T. DeVita, Jr., M.D.

DATE AND PLACE OF BIRTH: March 7, 1935, Bronx, New York

EDUCATION: 1957 - B.S. (Chemistry), College of William and Mary, Williamsburg, Virginia

1961 - M.D. (with distinction), The George Washington University School of Medicine, Washington, D.C.

POSITIONS HELD:

1961 - 1962	Internship, University of Michigan Medical Center, Ann Arbor, Michigan
1962 - 1963	Residency in Medicine, The George Washington University Medical Service, District of Columbia General Hospital, Washington, D.C.
1963 - 1965	Clinical Associate, Laboratory of Chemical Pharmacology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland
1965 - 1966	Senior Residency in Medicine, Yale-New Haven Medical Center, New Haven, Connecticut
1966 - 1968	Senior Investigator, Solid Tumor Service, Medicine Branch, National Cancer Institute, Bethesda, Maryland
1968 - 1971	Head, Solid Tumor Service, Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland
1971 - 1974	Chief, Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland
1974 - 1980	Director, Division of Cancer Treatment, National Cancer Institute, National Institute of Health, Bethesda, Maryland
1975 --	Clinical Director, National Cancer Institute, National Institutes of Health, Bethesda, Maryland
1980 --	Appointed by the President as Director, National Cancer Institute, National Cancer Program, National Institutes of Health, Bethesda, Maryland

ACADEMIC APPOINTMENTS:

1971 - 1975	Associate Professor of Medicine, The George Washington University School of Medicine, Washington, D.C.
1975 --	Professor of Medicine, The George Washington University School of Medicine, Washington, D.C.
1985 --	Consulting Medical Staff, Internal Medicine/Medical Oncology Department, National Naval Medical Center, Bethesda, Maryland

EDITORIAL BOARDS:

1968 - 1974	Associate Editor, *Journal of the National Cancer Institute*
1970 - 1974	Scientific Editor, *Cancer Chemotherapy Reports*
1975 --	Advisory Editor, *International Journal of Radiation Oncology, Biology and Physics*
1977 - 1981	Associate Editor, Editorial Advisory Board, *Cancer Research*
1978 - 1980	Member, Board of Medical/Scientific Consultants, *Cancer Nursing*
1979 - 1984	Member, Editorial Board, *Seminars in Oncology*
1979 - 1981	Associate Editor, *The American Journal of Medicine*
1977 --	Member, Board of Scientific Council, *Cancer Chemotherapy and Pharmacology*
1977 --	Associate Editor, *Cancer Clinical Trials*
1977 - 1978	Member, Editorial Board, American Federation of Clinical Oncologic Societies
1979 - 1980	Member, Editorial Board, American College of Physicians (A.C.P.), Audio Cassette Program
1980 --	Member, Editorial Board, *Your Patient and Cancer*
1980 --	Member, Editorial Board, *International Journal of Radiation Oncology, Biology and Physics*
1980 --	Member, Editorial Advisory Board, *Breast Cancer Research and Treatment*
1981 --	Member, Editorial Board, *Cancer Research*
1981 --	Member, Editorial Board, *Gynecologic Oncology*
1981 --	Member, Editorial Board, *Hematological Oncology*
1982 --	Member, Editorial Board, *Physicians' Drug Alert*
1982 --	Member, Editorial Board, *Cancer Investigation*
1982 --	Member, Editorial Board, *Journal of Clinical Oncology*
1983 --	Associate Editor, *Cancer Investigation*
1983 --	Associate Editor, *American Journal of Medicine*
1983 --	Advisory Editor, *Hospital Practice*
1984 --	Member, Editorial Board, Cable Health Network
1985 --	Member, Editorial Advisory Committee, *Core Journals in Hemato-Oncology*
1986 --	Guest Editorial Member (meritorious), *Japanese Journal of Cancer Research*

COMMITTEES AND OTHER OFFICES :

1968 - 1970	Councilman, Assembly of Scientists of the National Cancer Institute, National Institutes of Health
1970	Clinical Research Committee, National Cancer Institute
1972	Chairman, Program Committee, American Society of Clinical Oncology, Inc.
1973 - 1976	Board of Directors, American Society of Clinical Oncology, Inc.
1974 --	Member, Albert Lasker Medical Research Awards Jury
1975	American College of Surgeons' Commission on Cancer, Committee on Patient Care and Research
1975 - 1976	Advisory Committee on Clinical Investigations II - Chemotherapy and Hematology, American Cancer Society, Inc.
1975	Publications Committee, American Society of Hematology
1976	Member, Expert Advisory Panel, World Health Organization (WHO)
1976 - 1979	Member, Board of Directors, American Association for Cancer Research
1977 - 1978	President, American Society of Clinical Oncology
1976	Chairman, Treatment Committee of the French-American Agreement, Union Against Cancer
1976 --	Member, Jeffrey A. Gottlieb Memorial Award Committee, University of Texas System Cancer Center
1978 - 1979	Chairman, Special Membership Committee, American Association for Cancer Research
1979 - 1982	Member, Panel of Consultants on Clinical Oncology, International
1981 - 1985	Member, Awards Assembly of the General Motors Cancer Research Foundation
1983 --	Member, Armand Hammer Cancer Award Committee
1984 --	Member, Advisory Council, General Motors Cancer Research Foundation

CERTIFICATION SPECIALTY BOARDS:

1961	Diplomate, National Board of Medical Examiners
1968	Diplomate, American Board of Internal Medicine
1972	Diplomate, subspecialty of Hematology, American Board of Internal Medicine
1974	Diplomate, subspecialty of Medical Oncology, American Board of Internal Medicine
1974	Recertified, American Board of Internal Medicine

PROFESSIONAL SOCIETIES :

Fellow, American College Physicians
Member, American Society of Hematology
Member, American Society of Clinical Oncology

	Member, American Association for Cancer Research
	Member, American Federation for Clinical Research
1972	Elected, American Society for Clinical Investigations
1976	Member, Society of Surgical Oncology (The James Ewing Society)
1985	Elected, Institute of Medicine, National Academy of Sciences

HONORS AND AWARDS:

	Phi Beta Kapp
	Alpha Omega Alpha Medical Honor Society
	Smith-Reed-Russell Medical Honor Society
1959	Research Fellow with Adrian Hogben, Mount Desert Island Biological Laboratory, Bar Harbor, Maine
1970	"Oren del Sol en el Grando de Official" awarded by the Government of Peru
1972	Visiting Professorship of Medicine (July-August), Stanford University School of Medicine
1972	Albert and Mary Lasker Medical Research Award
1973	First Annual Clowes Lecture, Roswell Park Memorial Institute
1975	Department of Health, Education and Welfare Superior Service Award
1976	Esther Langer Award
1976	Alumni Medallion, The College of William and Mary
1976	Jeffrey Gottlieb Award
1978	Bronze Medal, American Society for Therapeutic Radiology
1979	Karnofsky Prize and Lecture
1980	Griffuel Prize, Association for the Department of Research on Cancer, Paris
1982	James Ewing Award, The Society of Surgical Oncology (The James Ewing Society)
1982	Honorary Doctor of Science, The College of William and Mary
1983	Alumni Achievement Award, The George Washington University
1983	Honorary Membership, Society of Gynecologic Oncology
1983	Honorary Membership, Japanese Cancer Society
1983	Honorary Fellow, American College of Radiology
1983	Memorial Sloan-Kettering Cancer Center Award
1983	Distinguished Service Medal, United States Public Health Service
1983	Honorary Doctor of Science, Ohio State University
1984	Honorary Doctor of Science, The George Washington University School of Medicine
1984	Meyer and Anna Prentiss Award
1984	Member, Honorary Board, Montgomery Hospice Society
1984	Second Emmanuel Cancer Foundation Award

1985	Pierluigi Nervi Award, Rome, Italy
1985	Medal of Honor, American Cancer Society
1985	The Barbara Bohen Pfeifer Award, American-Italian Foundation for Cancer Research
1985	Stratton Lecture, American Society of Hematology
1985	Leukemia Research Fund Lecture, London

MARITAL STATUS: Married, two children

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PROGRESS IN PAST YEAR

Dr. DeVita. This has been a very exciting year in the cancer program, and the story, I think, is one of unprecedented understanding of what makes a cancer cell a malignant cell. One of the features that we have begun to realize about a cancer cell is that it is not omnipotent; it is a cell that is somewhat confused, that uses the normal genetic mechanisms of the body in an aberrant way.

It appears that after the cell is exposed to a cancer causing insult that it sets off a cascade of genetic events that lead to the uncontrolled growth of the cell. This cascade of genetic events is under the control of the genes that we have been telling you about for the last several years, the oncogenes, that were probably normal components of development for humans.

The interesting thing that has happened in the last year has been that while a year or two ago we were discovering more oncogenes, the emphasis has switched to understanding the products of the oncogenes or, even further than that, understanding the switches that control the genes that make the products. Using the technology that is available today, it is really quite easy now to examine the genetic material on the flanks of these genes, to uncover the switches that control them with the hope that we can turn these on and off.

Another very interesting turn of events in the past year in reference to oncogenes is they have gone from the laboratory dish back into the animals. We are now able to take these oncogenes and inject them into a fertilized egg and put a signal switch on the end of the genes so that every cell in the body of the grown animal from that fertilized egg will have the gene, and it can be turned on and off. Mice grown from fertilized eggs heated this way are referred to as transgenic mice. If one puts in several oncogenes, one can turn them on in sequence. This allows us to examine ways to shut them off as a way of preventing cancer or turn them down as a way of treating cancer.

There is a unity of thinking also coming to the cancer field that was not apparent before. For example, we know that cancer is caused by exposure to initiators on one hand and materials called promoters on the other, the latter affecting the late stage of carcinogenesis.

We are now finding out that promoters act in many cases at the same sites that oncogene products are acting, so there is an internal unity here between the cause of cancer and promoters.

We also recently learned this year as a matter of fact—that promoters can induce resistance in the cell to the cancer drugs we use.

This year we have uncovered what we are calling the drug resistance genes. These are genes that are responsible for the cell being able to destroy some of the best anti-cancer drugs. It turns out that they are genes that are normally used by the body to interact with environmental toxins and carcinogens. When the cell becomes malignant—particularly the cells of cancers like lung and colon cancer, the kinds that are exposed to the environment they already have the tools on board to chop up some of our better anti-cancer drugs.

There is another new area that I would like to mention that I think is very exciting. It is emerging this year. We are referring to it as the new pathology. In the past we identified cancer cells under a microscope as coming from one or another tissue—lung, breast, lymph node, so forth. And we would often select the therapy based on that pathology.

What is coming now is what we call the new pathology which is the characterization of the cancer cell. You take a cell and look at how it expresses its genes, or use monoclonal antibodies to look at its surface. We call that genotyping, phenotyping, and looking at gene expression. A very startling example in the clinic within the past year is a tumor that was not responsive to treatment, was found to have a similar pattern of gene expression to a tumor that is responsive to treatment. When the treatment for that tumor was applied in the first tumor, it responded well to the therapy. Thus this new pathology will enable us to locate tumors and treat them successfully which had previously been thought to be refractory to treatment.

As a matter of fact, our ability to characterize cells has reached the point where, in the latest issue of Science Magazine Dr. Renat Dulbecco, Nobel laureate in medicine in 1975 and a generally conservative gentleman from the Salk Institute in California, has suggested that we are now in position to map the human genome from beginning to end, which would be indeed a very important advance for all biomedical research.

Before I close, Mr. Chairman, let me just cite a few of the practical things that have happened in the past year that you may be interested in, and describe what we plan to do next year in the areas of treatment and prevention.

First of all, in the area of treatment we have had some very positive results in the past year. You may have heard of the therapy developed by Dr. Steven Rosenberg, the Interleukin-2 plus LAK cell therapy, which is working extremely well in tumors like kidney cancer, melanoma and colon cancer. We have monoclonal antibodies in clinical trials that are working against melanoma. They are also being tested against colon cancer, breast cancer and lymphomas.

We have had two positive studies this year in the adjuvant situation; that is, drugs given after surgery, in common tumors, lung cancer and colon cancer. We have had two positive studies in patients with advanced metastatic cancer that are very interesting, advanced bladder cancer, and head and neck cancer. And we have new exciting drugs that are going into clinical testing.

In prevention, we have told you in past years we have some 26 clinical trials under way looking at ways to prevent cancer in high risk populations. This year we are initiating what we are calling the Women's Health Study, which is a low fat diet compared to a normal diet, to see if we can reduce breast cancer incidence in women who are known to be at high risk of developing breast cancer.

We have studies already planned for fiscal year 1987 to test ways of blocking metastases using a fragment of a material called laminin that blocks the cancer cell's ability to bind to membranes it has to go through to travel to other parts of the body. We will expand the molecular characterization I described to more common tumors.

There are studies under way that will reach clinical trial to reverse the drug resistance that I referred to earlier, particularly of a monoclonal antibody to a protein on the surface of the cell that is mediated by these resistance genes.

And, of course, we plan on expanding the LAK cell project, depending on how the results go this year.

All in all, it has been exciting Mr. Chairman. I would like to emphasize that all these practical things that I have mentioned have stemmed from the extensive support for basic research that the National Cancer Institute has, with your help, put into the research establishments of this country in the last two decades.

The budget request for the Cancer Institute for Fiscal Year 1987 is $1,158,089,000. Mr. Chairman, that concludes my remarks, and I would be happy to answer questions from you and the Committee.

BUDGET HISTORY

Mr. NATCHER. Thank you, Dr. DeVita.

Dr. DeVita, I recall a number of years ago when Dr. Shannon was Director of the National Institutes of Health. One day we asked him if he could use a billion dollars for cancer research. Back in those days the amount that we were appropriating for cancer research was a little over $200 million, between $200 million and $300 million. And we wanted to know if he could use a billion dollars. He said he could not. At that time he said, "I cannot use a billion dollars. It is too much. We cannot handle that kind of money at this particular time."

As you know, Dr. DeVita, we have moved along now in the last several years. We appropriated $1,258,159,000 for the National Cancer Institute for Fiscal Year 1986, I believe that is the exact amount in the Cancer Institute.

For the National Institutes of Health, we appropriated $5,500,000,000. I round it out. That is what we agreed upon and the President signed into law.

You know, it is right hard, Dr. DeVita, for us on this Subcommittee to attend an overview hearing on the entire budget when they say to us that we want a 16 percent increase in foreign aid and a 13 percent increase in defense, but we want to cut the National Institutes of Health. It is right hard for us to understand, Dr. DeVita. We understand on this Committee, and we know that with a national debt of over two trillion dollars, it requires another $200 billion to pay the interest on the debt, we know the seriousness of that situation. We know it is serious, the most serious problem that we have.

But when they come in, Dr. DeVita, and say we want to cut cancer, heart and stroke research, we do not agree, Dr. DeVita. I do not. I do not agree. And I think it is a mistake. We ought to spend our money for the health of the people in this country and for education. That is where we ought to spend most of our money. And when we do, we will continue to have the greatest country in the world.

BASIC RESEARCH

I just wanted to point those figures out to you, Dr. DeVita. You are acquainted with those figures. Dr. DeVita, do you still consider basic research to be the top priority of the National Cancer Institute?

Dr. DEVITA. Yes. The support for basic research has always been and for the foreseeable future will be the number one priority for cancer.

Mr. NATCHER. Are we right in thinking that the primary vehicle for support of basic research is the investigator initiated research grant?

Dr. DEVITA. Yes, it is, but I have an opinion to give on this, Mr. Natcher that would depart somewhat from——

Mr. NATCHER. Well, go ahead, Doctor, and tell us what you have in mind.

Dr. DEVITA. As science is moving along and becoming more complicated, one has to use many mechanisms to support basic research besides the research project grant.

For example the Cancer Institute is sponsoring a rather large high-speed computer, a super computer, that is an instrument for part of an experiment in basic research. You cannot do this with a research project grant.

I think that the only danger of saying yes to the second question is that we assume that no basic research is supported by any other instrument. It is much safer to say that our number one priority is in fact the support for basic research not the instrument.

Mr. NATCHER. Dr. DeVita, do you believe that Congress is forcing you to put too large a share of your resources into investigator initiated research grants?

Dr. DEVITA. Well, I think, Mr. Natcher, that we would probably wind up doing the same thing in the sense that if we both agree support of basic research is number one, at the end of the year we would come out showing that in our budget. In years when we were not fixed on numbers of grants we did just that. So I guess as any program manager, one chafes a little bit when the budget or grant lines are a little bit too tight so that we cannot move resources around in a time when science is moving so fast.

The answer is we appreciate the Committee's emphasis in this area and do not disagree with it, with the caveats that I have already mentioned.

FLEXIBILITY

Mr. NATCHER. Do you feel that you, as the Director of the National Cancer Institute, have the flexibility to allocate your resources to the programs where they will be used most effectively, generally speaking? Would you say that would be correct, Doctor?

Dr. DEVITA. The numbers do get us into some difficulty, Mr. Natcher. The Committee has always been responsive to our requests for reprogramming, and we can make those kinds of requests. But as I indicated earlier, if something happens, like Dr. Rosenberg's LAK cell therapy project, in the middle of the year and we have to make some immediate shifts of resources, it would be ideal from the manager's point of view to be able to move resources quickly from one pocket to another without having to go through too many administrative steps. I am not a great fan of bureaucracies, I am afraid.

Mr. NATCHER. Are restrictions placed on you by, one, authorizing legislation; two, appropriations acts; three, the Office of Management and Budget; four, the Department of Health and Human Services; five, the Public Health Service; six, the Director of NIH; or the National Cancer Advisory Board limiting your effectiveness as commander-in-chief on the war on cancer?

What would you say about that, Dr. DeVita?

Dr. DEVITA. I would say to some degree, yes, in all cases, but that is——

Mr. NATCHER. Go ahead and talk to that, Doctor.

Dr. DEVITA. You know, it is unavoidable in the sense that we are all part of the effort. As we come and testify before Congress to approve our budget we recognize that we have to answer to the Congress and to all those organizations you mentioned.

What I was saying before is that if we can minimize the interaction for less than major policy issues it is always better. The National Cancer Advisory Board provides relatively few restrictions. At the moment however, the way the budget is apportioned, there are numbers of controls that require steps through the NIH, and the OMB that can conceivably slow us down.

NUMBER OF GRANTS

Mr. NATCHER. You know, at times, Doctor, we on this Subcommittee and on the full Committee on Appropriations are accused of taking too good a care of you. We have people say that. Some of the other institutes, and I am going to meet with a group this week, they say do not forget us. We are there too. We are one of 11 institutes. Do not forget us. Do not put it all into cancer research.

You know, Doctor, we hear that from time to time on this Subcommittee. We try to treat them all fair. We believe in all of them, Doctor.

I was just wondering now what your answer would be to these items that I have just enumerated, and I understand what you are talking about. The Administration is proposing language to remove the requirement for NIH to support no fewer than 6,100 new and competing research projects in 1986.

They are also proposing language to require that NIH and the Alcohol, Drug Abuse, Mental Health Administration support no fewer than 19,400 total grants in 1987.

If you will, Doctor, give us your views on these two proposals. And before you do, Doctor, you know, you read a lot in the press and you watch television and you hear about 6,100 and 6,200 and this, that and the other. You know, on this Subcommittee, Doctor, we have been working for years. When you talk about 6,100, you are looking at the Committee that made it 6,100. When you talk about 6,200, you are looking at the Committee that made it 6,200.

Our Subcommittee members are all able people, Doctor. They work hard. That is where you get your 6,100 and 6,200. You know what I am talking about.

Dr. DEVITA. Yes, sir.

Mr. NATCHER. Doctor, go ahead now and talk to us about this question.

Dr. DEVITA. Well, I generally think the movement toward a broader target is better than fixing on, say, 6,100 competing grants. The movement toward the total grant pool, if one is going to focus on anything, gives a little bit more flexibility.

Again, as long as we say—and our feet are held to the fire at the end of any fiscal year—that basic research is our number one priority, then I believe that a broader target provides a little bit more flexibility to choose amongst competing and noncompeting grants.

A lot of new investigators come in through the competing grant pool, but a lot of new research that I spoke about in my opening comments, was done by people who have been supported in the non-competing grant pool. And so a lot of new research goes on in non-competing grants. I generally prefer the stabilization at the broader level.

I would add just one little point. One of the reasons that I am able to come here and tell you that we now can look inside the cancer cell and watch the machine work is because of some of the Nobel prize winning work that was done in the early '70s, and one of these discoveries was made under a center core grant. The investigator was very young and had not yet established himself, and the center core grant provided the resources so that the investigator could get started and he won a Nobel prize. You cannot always predict where a discovery is going to come from, and that is the genesis of my comment about focusing too narrowly on competing research project grants. That is why I like 18,000 better than 6,000 in terms of a broad target. We have debated this at length in all the corridors within our own institutions, and I have had my chance to say what I feel. To me, the broader base that you are supporting in terms of basic research, the better, it is.

PROGRAM BALANCE

Mr. NATCHER. Dr. DeVita, do you believe that within available resources we should be placing greater emphasis on prevention, control, clinical trials and dissemination of the latest treatment methods as opposed to more basic research?

Dr. DEVITA. No. I still think we got where we are by basic research, Mr. Natcher, and I would not change that for a moment.

What is happening is a rather exciting phase of cancer research. For example, the new pathology that I described not even two years ago was laboratory molecular biology, totally basic research. This year it is a clinical tool being applied to the treatment of tumors in human beings, skipping rodents and other species. It has gone from the laboratory to the clinic so fast, and it is applicable so fast that the danger of missing these kinds of opportunities.

So you have to support basic research; that is where all the good stuff is coming from. But you cannot ignore the applications side of it, either in treatment or prevention; otherwise, we will miss the opportunity that has been created by the basic research support.

It is a matter of balance within the program, and we always strike for a balance. If we have an opportunity, we push it. The LAK cell project, which I will come back to over and over again, because it was an opportunity that presented itself to us last year, is a good example where we have had to move very rapidly. We have in fact done some things to move it along.

CANCER STATISTICS

Mr. Natcher. Doctor, is it true that the number of new cases of cancer and the number of deaths from cancer in this country continue to rise each year?

Dr. DeVita. If you look at it on the basis of population per hundred thousand, the incidence is rising faster than the mortality, which is good news in the sense that you are obviously curing more people than are getting the cancer.

But as I have indicated in the past, Mr. Chairman, it is not terribly useful to look at all cases combined. One has to look at them a tumor at a time. You can look at the incidence of a cancer, the mortality from that cancer, and the survival rate from that cancer, which is what we have been doing every year at the Cancer Institute since the SEER program reached its maturity about three years ago.

We are now able to look at a decade, split the decade in half, compare the first half to the second half, and make comparisons. Of course, this is the source of the controversy that you have heard about from time to time. Since we make the data available, it can be analyzed and interpreted by everybody.

The answer to your question is that incidence is rising, largely due to lung cancer which dwarfs the rise of incidence in other cancers. Mortality is falling if one moves lung cancer out of the statistics, and if one looks at specific cancers, we have some very interesting combinations. For example, the incidence of colon cancer is rising; the mortality from colon cancer is falling, and the survival rate is increasing. All that indicates better management of the cancer patient, better treatment, better diagnosis.

We do not know why exactly it is happening because there has been no real major change in our management that we can identify in the past ten years. But nonetheless, it is a real fact, something good is happening in colon cancer.

Lung cancer does not work that way; pancreas cancer does not work that way. For other kinds of cancers, it is a little bit different.

PROGRESS IN CANCER RESEARCH

Mr. Natcher. Doctor, how long have you been the Director of the National Cancer Institute?

Dr. DeVita. I was appointed in July of 1980, Mr. Natcher.

Mr. Natcher. Do you feel generally better today than you did when you first took over as Director? Do you feel now that we are moving along, Doctor?

Dr. DeVita. Mr. Natcher, I have never seen anything like it in my life.

Mr. Natcher. Right at this point in the record now, Doctor, when you get the transcript back—you know, we have to defend this on the floor, the amount we are going to approve for your Institute and for the National Institutes generally, not in great detail but a good, sound statement in there in answer to that question, Doctor.

Dr. DeVita. Certainly.

Mr. Natcher. It would help us.

Dr. DeVita. I would be pleased.

[Information follows:]

PROGRESS IN CANCER

Mr. Natcher, I have never seen anything like it in my life. Indeed, the pace of progress in cancer research has been and continues to be remarkable.

I was appointed Director of the National Cancer Institute (NCI) in 1980. At my first news conference as Director, I pointed out that doctors were curing 41 percent of all cancers. Today we can say that 50 percent of all serious cancers are curable.

In the past five to six years there has been tremendous progress against cancer. We are now at the most productive period in the history of cancer research and are able to transfer new knowledge of cancer biology rapidly to the clinic. This is possible through a nationwide network of centers, cooperative groups of researchers, and community physicians. The network has been streamlined over the past few years.

In 1980, we knew of the discovery of oncogenes -- the genes associated with transforming a normal cell to cancer. But we had no idea of the implications of these findings. Basic research has continued to elucidate the cancer story of oncogenes and their counterparts, proto-oncogenes, involved in our normal growth and development. We have learned that cancer cells are renegades. Instead of being indestructible, they appear to be immature, somewhat confused cells, running on second-rate genetic machinery. Today, research has given us an unprecedented understanding of the cancer cell and has led us to fundamentally change how we approach preventing and treating cancer.

Although cancer is over 100 different diseases, we now feel certain they share some basic mechanisms that set off the disease. We have already exploited some of these data at the clinical level. All cancers are becoming increasingly vulnerable as researchers probe further into the cancer process and move closer to the ultimate successful prevention and treatment of the disease.

Even before full knowledge of the cancer blueprint is available, with what we have in hand, we are making rapid headway to prevent and treat cancer. Already, based on the new cancer biology, major efforts are underway to prevent cancer; to reverse the cancer process by nudging a transformed cell back to normal; to employ the exquisite network of our immune system to defend against cancer; to refine treatment and destroy more selectively cancer cells; and to block metastasis -- the ability of cancer cells to spread and kill.

Some examples of how the National Cancer Program has progressed in the last five or six years include the following:

- Researchers have been unraveling the multi-step cancer process and now have discovered more than 30 oncogenes that are related to transformation of cells to cancer. Knowledge of cancer biology today has brought together various pieces of the cancer puzzle. Once seemingly diverse research concepts from virology, chemical carcinogenesis, biology, and genetics have come together with startling unity.

- A new development, important for streamlining studies of oncogenes, is a technique called "marching down the chromosome." Scientists isolate the ends of large DNA fragments and use them to probe and isolate additional ends of DNA further along the chromosome. With this new method, much information is obtained quickly so that new genes can be identified, compared and sequenced.

- A few years ago, research focused on the discovery of oncogenes. The field has now moved toward also understanding the products that oncogenes make and the "control switches" that turn these genes on and off. These switches can be either next to an oncogene -- called flanking sequences of DNA -- or be removed some distance from it. This research provides vital new information for preventing cancer -- for turning its switches "off."

- The study of oncogenes and their control is also moving from the laboratory dish to studies in live animals. It is now possible to make combinations of different oncogenes and their flanking DNA sequences in the laboratory, then inject these "foreign" genes into fertilized mouse eggs and produce mice (transgenic mice) in which every cell contains the foreign genes. The use of transgenic mice is an invaluable tool to examine ways to interrupt oncogene function and prevent or reverse the malignant process.

- At the clinical level, oncogenes influence the aggressiveness of cancer cells and their ability to spread and invade distant, vital organs, causing death. Activation of more than one oncogene, and the presence of many copies of a single oncogene (gene amplification) have been closely linked with this metastatic process in lung, colon, and breast cancer.

- Recombinant DNA techniques and monoclonal antibody technologies that have contributed so much to unfolding the cancer story, now hold enormous promise for rapidly diagnosing and characterizing tumors and for treating patients. Gene technologies are promising not only for identifying populations at high risk for cancer, but also will result in more targeted prevention programs and effective screening programs for early detection and prompt treatment.

- Gene technology has been increasingly applied to cancer diagnosis. Specific DNA "probes" are now used to identify genetic alterations in tumor tissue. The presence of oncogenes can be detected and the amount of their gene products measured.

- Capitalizing on information from basic research that cancer is a multi-stage process, NCI is now investigating practical ways to prevent cancer by interfering with the late, "promotion" stages of the process, perhaps even by blocking the activity of oncogenes. An extensive research program on diet and cancer, for example, is underway. NCI is recommending dietary modifications such as increased fiber and decreased fat in the diet as part of a major Prevention Awareness Program.

- In addition to dietary modification, NCI is exploring chemoprevention as a way of interfering with the promotion stages of the cancer-causing process. Twenty-six human chemoprevention studies are now underway, testing pure chemicals or micronutrients in precise doses to determine preventive effects. If even one of these studies should prove successful, a substantial number of cancers would be preventable.

- Progress continues in surgery, radiotherapy, and chemotherapy as effective treatments for many cancer patients. This year, for example, lumpectomy followed by radiation for early-stage breast cancer was reported to be as effective as mastectomy; progress continued in arming monoclonal antibodies with radioisotopes; and adjuvant chemotherapy (use of anticancer drugs to prevent cancer recurrence by eradicating microscopic spread of tumor cells) gained new recognition. Positive adjuvant treatment studies in breast cancer, rectal cancer, colon cancer, and adenocarcinoma of the lung were reported during 1985. Such adjuvant treatment of cancers widely applied could be expected to save the lives of 22,000 Americans each year.

- A major obstacle to curing cancer with drugs has been the resistance that certain cancer cells develop to the drugs. Findings this year suggest that the basic process of cell transformation to cancer may at the same time amplify a cell's defenses against toxic substances so that it strongly resists foreign agents such as anticancer drugs. For the first time, this research establishes a link between drug resistance and the fundamental cancer transformation process.

- A major, achievable goal in cancer treatment will be to characterize oncogene products and develop new strategies to inhibit their production or action. There is already a startling and practical clinical example where selection of therapy based on patterns of oncogene expression has led to improved results. Such approaches are being explored in a variety of tumors.

- This year, a very promising trial of biologicals was reported, using adoptive immunotherapy -- the transfer of anticancer immune cells directly to the cancer patient. Early results in patients with advanced cancers who were treated by these IL-2 lymphokine activated killer (LAK) cells and very high doses of IL-2 have been most encouraging, especially in cancers of the kidney, the colon, and melanoma. The NCI is now testing this treatment across the country in its network of cancer centers and cooperative clinical groups.

- Significant gains in survival have been maintained for many cancer sites including Hodgkin's Disease, the major cancers of children, and testicular cancer. This year, a worldwide review of breast cancer clinical trials indicated that appropriate use of chemotherapy in patients of high risk for recurrence could reduce early mortality from this disease by 25 percent in women under 50 years of age, and, nationally, we are beginning to see a decrease in breast cancer mortality rates in this age group.

- Meantime, NCI continues to track the incidence, survival and mortality rates of cancer in the United States. The Surveillance, Epidemiology, and End Results (SEER) program, which began in 1973, has now been in operation for a sufficient time to allow consistent estimates of cancer patient survival changes. The steady progress now being made in cancer treatment is beginning to have an impact on a number of cancers and on national cancer survival statistics. Five-year relative survival rates have reached 50 percent for patients with serious cancers.

- Recently there have been major advances in the development of entirely new approaches to cancer treatment. These approaches are based on the knowledge and tools of modern molecular biology, immunology, and genetics that have provided new targets for cancer therapy.

- NCI is funding 34 tobacco-related intervention studies -- involving more than five million people -- to find ways of reducing smoking in large populations of Americans. Among those targeted are adolescents, minorities, women, and smokeless tobacco users. (This year for the first time in 50 years, the incidence of lung cancer decreased in white males.)

- In 1984, we announced goals for the year 2000 -- to cut current cancer mortality rates by 50 percent by that date. This will be accomplished through major efforts in cancer prevention and encouraging the receipt of state-of-the-art treatment by all cancer patients.

- Future gains against cancer will depend to an important degree on solving the problem of excess cancers and cancer deaths among minority populations. As a result of this problem, pointed up dramatically in recent years by NCI's SEER program, the NCI is sponsoring a special initiative to address cancer problems in minorities, with early emphasis on black Americans.

- The NCI has initiated a number of programs to speed the transfer of new advances from basic and clinical research into the community at large. These efforts include the network of cancer centers and cooperative groups of clinical researchers, which are established around the country; the Community Clinical Oncology Program (CCOP), which connects practicing physicians with research programs at the cancer centers and the cooperative groups; and Physicians' Data Query (PDQ), which is a computerized information system that allows physicians nationwide to easily and quickly access the most up-to-date information about cancer treatment and clinical trials.

- This year, there have also been major advances in imaging technology. Investigators have now used sodium and phosphorous imaging techniques in Magnetic Resonance Imaging (MRI) to distinguish cancer from benign tumors. MRI is proving useful for defining the extent of tumor involvement of lung, liver, brain, and other organs.

- Using recombinant DNA technology, the genes of several body proteins, interferon, IL-2, and, most recently, tumor necrosis factor (TNF), have been cloned, permitting preparation of these important substances on a scale large enough to conduct clinical studies. These factors are all being tested now for their antitumor effects in cancer patients.

- Studies are underway of agents that can make the cell become more mature, or non-cancerous. The retinoids, analogs of vitamin A, have produced clinical responses in patients with preleukemias, acute promyelocytic leukemia, and early cancer of the mouth, skin and cervix.

- An area of high-priority research is the process of metastasis. During the past year, small fragments of laminin have been prepared which can block the cancer cells' laminin receptor and so prevent attachment to laminin on the vessel's basement membrane. Laminin fragments have successfully prevented tumor cell spread in experimental animals. This novel treatment will begin clinical trials in patients this year.

- Human cells from small cell lung cancers produce growth factors that are capable of stimulating the cancer's own growth. Researchers have identified one of these growth factors, bombesin, and monoclonal antibodies have been designed against it. A novel clinical trial using these antibodies in patients with small cell lung cancer is beginning.

- Basic cancer research continues to have major spin-offs for new knowledge in other diseases as well (most recently, cystic fibrosis and multiple sclerosis).

- Last year, NCI made important contributions in many areas of AIDS research. These included advances in understanding the molecular biology of human T-cell lymphotropic virus-III (HTLV-III), the cause of AIDS; understanding the natural history and transmission of AIDS; identifying potential new therapies for the disease; and developing a vaccine and an animal model for the disease.

These highlights are just some of the reasons why I feel more optimistic than ever about the National Cancer Program, Mr. Chairman.

Mr. NATCHER. Mr. Conte, I yield to you.

Mr. CONTE. Dr. DeVita, it is nice to have you here before the Committee.

Dr. DEVITA. Thank you.

Mr. CONTE. Yesterday we had Dr. Fauci here and Dr. Gallo who has made all these great breakthroughs. Dr. DeVita, Mr. Amoruso.

Dr. DEVITA. Not bad, right?

Mr. CONTE. Not bad.

Dr. DEVITA. It was truly accidental. [Laughter.]

Mr. CONTE. It is fantastic. I am not going to say any more.

Dr. DEVITA. My mother would be proud of you.

NUTRITION

Mr. CONTE. What did you have for breakfast this morning, Doctor?

Dr. DEVITA. My usual, sir; bran muffins.

Mr. CONTE. Through your work, all of us have come to recognize the importance of the diet as a prevention of disease, specifically cancer. What dietary changes would you like to see Americans make and what may be some of your upcoming recommendations to the American public?

Dr. DEVITA. Well, we have made recommendations to the American public. They have been the source of some controversy, which does not make us unhappy. When one deals in this field, you tend to generate controversy.

Let me just step back, if I can, Mr. Conte, and say that in 1979 several committees of Congress criticized the Cancer Institute for not putting enough emphasis on the role of diet in cancer causation. And in 1980 after my appointment, we decided to make some changes. I went out and recruited Dr. Peter Greenwald who is the head of our prevention program at the Cancer Institute, and we began to make plans to do research in diet and cancer to a greater degree.

By 1982 we were doing this, and we found out that you could not talk about how you were doing the research in a public forum, as we often do, without the American people asking you what they should do in the interim as you do more research.

So in 1982 we began to develop a prevention awareness program after a survey of the American people showed that they did not really know they could do things themselves that might be helpful.

In 1984 Secretary Heckler launched this prevention awareness program which included dietary recommendations. Since in most countries where they eat less fat and more fiber, they have a lower incidence of some kinds of common cancers; the prevention awareness program recommended that we should aim for less fat and more fiber in the American diet. Since we had been told, in the intervening two years, that one of the problems with making those kinds of recommendations is that it does not mean anything to anybody unless you translate it to understandable terms, we actually put numbers on them. We said it looks like 30 percent of your calories from fat or less, compared to 40 percent of your calories from fat was better, and that if the American people doubled the fiber intake we would approximate the fiber intake of countries where they have a lower incidence of colon cancer. So, we recommended a doubling of the fiber intake.

I have been very pleased since then because if you look around the marketplace, I think you are seeing the food industry in this country is trying very hard to respond to the desire of the American people to take advantage of these kinds of recommendations.

It has been controversial because the food industry has moved so fast. There is some question about whether or not the food labeling and advertising is appropriate, as you probably have heard. But by and large, I believe we are getting our message across, and I believe the people are very responsive.

DIET

Mr. CONTE. Are there any facts around to show what percentage of people get cancer because of their diet?

Dr. DEVITA. Well, the best data we have is a survey that showed that probably a third, maybe 30 percent of all cancers may be diet related: that is, about 30 percent are either preventable or caused by manipulations of the diet. If one looks at, say, cancer in Africa compared to cancer in the United States, or cancer in Japan compared to cancer in the United States, and then looks at the migratory populations and how they develop cancer, it looks like about a third or somewhat less than a third of all cancers may have a dietary factor involved.

Mr. CONTE. Do you think that hard data on the relationship between diet and cancer would be enough to promote changes in what we eat. After 20 or 30 years were still waging was on cigarettes; do you think we can move faster in changing our dietary habits than we did with cigarettes?

Dr. DEVITA. I do, mainly because the country really wants to do it. Second, you have to eat; you do not have to smoke. And although that might be viewed as food being addicting, which it is, cigarette smoking is in fact addicting, and it is very hard to get people to stop. The message is not that people have to stop eating, but that they should chose some different foods.

I should point out there has been considerable success in reducing the number of people who smoke; not enough, but considerable success. This year, in the SEER data, we were able to report for the first time that the incidence of lung cancer in white males has fallen significantly for the first time in 50 years, and that is related to smoking cessation.

Mr. CONTE. That is great.

INTERLEUKIN-2 THERAPY

Right about the time last year, Doctor, that we were bringing the Labor/HHS Conference Report to the floor, an exciting and promising new treatment for cancer was reported from your Institute involving the drug Interleukin-2, which you mention in your statement. Can you tell us how that therapy works?

Dr. DEVITA. Well, you will be pleased to know, in light of your opening comments, Mr. Conte, that Interleukin-2's first name was t-cell growth factor. It was discovered by Dr. Robert Gallo in 1976. It was one of his "minor" discoveries.

Dr. Rosenberg recognized its therapeutic potential and began working with it in rodents. It was not until about 1982 or perhaps '83 when the gene for Interleukin-2 was cloned—that is, it was possible through DNA recombinant technology to make buckets full of Interleukin-2—that we were able to take what were exciting results in animals and move them into people. And Dr. Rosenberg reported in December the first results in 25 patients showing rather dramatic results in kidney, and colon cancer and melanoma, and those results have only gotten better. As of last week, my count has about 71 patients treated, and, Mr. Conte, not a single patient with kidney cancer has failed to respond to this. I have never seen a treatment before that had a hundred percent response rate in any cancer that itself did not turn out to be a major treatment for that particular cancer.

Mr. Conte. How does that process work?

Dr. DeVita. Well, what we do is simple. Interleukin-2 is t-cell growth factor; it makes the normal t-lymphocytes in your body expand and grow and produce material. Dr. Rosenberg takes a cancer patient and removes their own t-cells, puts them in bottles in the laboratory, introduces Interleukin-2 and expands that population. Then he gives the patient Interleukin-2, very big doses; that is why you have to have DNA recombinant Interleukin-2. He gives the patient Interleukin-2 and then gives their cells back and keeps them expanded with the Interleukin-2 for a period of time, and then stops Interleukin-2 and those cells just die away.

Apparently, what happens is those cells go right to the tumor and release a material named cytolysin which is actually injected into the cancer cell and kills it. Some of the responses have been really rather dramatic. It represents a completely different kind of therapy. That is its advantage because it is a different approach, it can be used with any other therapy; it does not necessarily have to be used instead of other therapy.

I believe we may have seen the end of kidney cancer as a cause of death from what I can see so far.

Mr. Conte. With all the press that Dr. Rosenberg is getting, a lot of people want to find out if they are eligible. What advice would you give someone who wanted to get involved in one of these clinical trials?

Dr. DeVita. Well, it is not for everybody. For example, if you have a treatment that cures you now, obviously you should stay on that treatment. Anybody who can have their tumor removed quickly by surgery, fine; radiation, fine; chemotherapy that works, fine. But for certain people, like those with kidney cancer, it in fact represents a new dimension.

Now, we had to decide when to publish it, so we held it back until we had 25 patients and then published at that point. We knew it would get attention; it was unavoidable because the New England Journal of Medicine is monitored by the Associated Press and other wire services. It was an exciting new venture. But we were planning as soon as the article came out, to set up other centers to do the same work. And we have indeed contracted with six institutions to repeat, exactly as Dr. Rosenberg reported it, his study with the same tumors. And we have two or three others that are doing it in slightly different ways, also with NCI support, and some institutions that are willing to do it on their own if they are supplied with the protocol and Interleukin-2. So as of this discussion, there are about ten institutions able to do it, and for kidney cancer I think it is particularly worthwhile exploring going to one of those institutions.

AIDS

Mr. **Conte**. Last October I was proud to join with Dr. Gallo of NCI as a recipient of Boston University's Hubert Humphrey Cancer Research Award. Dr. Gallo has done an immense amount of work recently to enhance our knowledge about acquired immune deficiency syndrome. Just last week I read in the paper that Dr. Gallo and his team had identified the enzyme that allows the AIDS virus to reproduce itself. How big a breakthrough is that, and what things can we hope to see develop from this discovery?

Dr. **DeVita**. Well, this, I believe, is the work that was reported from Boston by Dr. Haseltine where they found there is one gene we call the tat gene which stands for transactivating transcription gene. It produces a protein that acts elsewhere in the cell as well as on the virus to accelerate its production in the cell. The importance of this is it gives us a place that we can target an agent to prevent the spread of the virus and also can lead to a greater understanding of how the virus gets control of cell machinery and why it is so specific for t-cells.

Mr. **Conte**. The Cancer Institute has been at the forefront of work to develop a vaccine for AIDS. How is that work progressing, and are you ready to begin testing some possible vaccines?

Dr. **DeVita**. The gentleman on my right, Dr. Fischinger, is the fellow responsible for that work, and he has some very interesting results.

We thought three years ago that we would have a vaccine for testing within three years and I think we will. Whether it works or not, perhaps Dr. Fischinger could answer that question, Mr. Conte.

Dr. **Fischinger**. I will be very happy to answer that question. The vaccine effort has been ongoing within the Institute for the last two years, and a number of groups are interactive, both intramurally and extramurally.

What has happened is that we have been able to isolate that molecule from the surface of the virus, which can induce an antibody that we think will protect against the infection with this virus.

The isolation of this molecule, which we call the major surface glycoprotein, has now been accomplished. This molecule has gone into a number of different species including monkeys, and we can report as of now that the right kind of antibody was induced. That is an antibody which will kill the virus in the test tube.

This has not been demonstrated before, and it does show that the path towards a vaccine development is now a little clearer. I think we are now on our way.

Mr. **Conte**. That is encouraging, most encouraging.

I think my time is up.

Mr. **Natcher**. All right, Mr. Early, I yield to you.

PROGRAM PRIORITIES

Mr. **Early**. Dr. DeVita, your overview states that "as the ongoing basic research—now at its most productive period in history—develops a comprehensive understanding of the step-wise cancer process, that new knowledge is put to work in practical ways that benefit the people."

Now, at its most productive period in history, Dr. DeVita, that is wonderful news. The bad news is this budget request, which is $73 million less than you had in the FY 86 bill. Are we taking advantage of that golden opportunity?

Dr. **DeVita**. Well, we are covering our high priorities. For example, the LAK cell project is a high priority, and we are reallocating resources to it so that we are not going to let the best programs not express themselves at the practical level to the best of our ability.

Mr. **Early**. We're certainly not going to put new knowledge to work in practical ways that benefit the people when program levels for the centers program, cooperative clinical group programs, cancer control and so on and so forth are declining, are we, Doctor?

Dr. **DeVita**. Not without readjustment of other programs.

Mr. **Early**. You know I am an advocate, as everyone is on this Committee is, of NIH, but really in the program the question that was directed to Dr. Bowen, I have never seen OMB take control of an agency, an individual agency like NIH, NCI, every one of you. And I really do not see the directors confronting or disagreeing with what you are being required to do and you have not got the money to do it.

Then you come in and you suggest to the Subcommittee that, well, the private sector is doing it. The private sector is doing it only at the Howard Hughes Institute; not because of NIH, not because of Frederickson. Don Frederickson would have never tolerated what is coming in here before this Committee. And you rationalize to justify the budget, in my opinion.

MOLECULAR CHARACTERIZATION

Dr. DeVita, can you explain to the Committee, and let me ask this question in parts, more about the molecular characterization cancer therapy for children; what kind of an impact it will have on survival? Is this a new development or will it become another focal point initiative of the NCI? And what should the next research step be?

Dr. **DeVita**. This is very exciting. It was discovered by a pediatrician who naturally turned to childhood malignancies with this tool. He happens to be a molecular biologist at the same time, the new breed of physician investigator.

He looked at the expression of oncogenes in a tumor called a neuroepithelioma—an uncommon tumor—and found that although it is related to another nerve tumor, neuroblastoma, that the gene expression was entirely different. And when he looked around for other tumors in the pediatric clinics that had similar gene expression, he found another tumor that is unrelated called Ewing's sarcoma, that expressed the same oncogenes in the same pattern. The reasoning then was let us use the therapy which works in Ewing's on neuroepithelioma, which had no therapy that worked; it was an incurable disease——

Mr. **Early**. Doctor, let me interrupt you. I do not want to be rude. You are getting into specifics. Let me be a bit more specific so the answer can be a little shorter.

Dr. **DeVita**. Sure.

Mr. **Early**. Are you encouraged? Do you think this has real potential?

Dr. **DeVita**. In the next year. We will explore whether what he has found in these two tumors is generally applicable to common tumors, and we think, our best guess is, it will be.

Mr. **Early**. Are funds and other staffing resources included in your '87 budget request for this?

Dr. **DeVita**. Since this came up very recently, we have not yet included it in the '87 budget. We will have to redirect some resources to the Pediatric Branch to do this.

Mr. **Early**. Would that not be a priority, Doctor? Is that not what you are supposed to be doing?

Dr. **DeVita**. Yes, indeed, Mr. Early. But, you know, it really is very recent, and at the time we were preparing the '87 budget, this information was not yet available.

Mr. **Early**. Do you know who is going to determine if it is important, Dr. DeVita? OMB. Boy, that is discouraging. That is really discouraging.

FLEXIBILITY

Doctor, tell me, you have been there since '80. Do you have the flexibility as Director of NCI that you had before OMB has taken it over?

Dr. **DeVita**. Well, I am worried about flexibility. I would argue that at any given level of budget, I accept whatever we have to accept, Mr. Early. We all get a chance to argue our case internally in terms of budget, and there is more to the Federal Government's budget than the NIH. I know that does not please you. But, in fact, we are able to argue our case for the budget.

Then we get a budget and——

Mr. **Early**. Yes, but you do not argue as good as Defense. Defense gets whatever they suggest. Defense gets more in Star Wars than you get—50 percent more than what you spend to fight every disease in the world. I do not accept that.

Dr. **DeVita**. We argue, as every department argues, you cannot support every agency with more under the current environment and still have anything left. At whatever budget level we receive, flexibility becomes very important and I am concerned about flexibility. I do not necessarily think it is just at OMB. I think any time you impose steps between the people who have the responsibility for putting a program in place, that is, you separate responsibility from authority, you slow down the process.

Mr. **Early**. I personally think OMB is laughing at you. I think OMB is throwing you in a category with everyone else. You are also in the also-rans. You are not unique. You are not accepting what the Chairman of this Committee has done for you since you began. He always says that NIH started with $73 million, now you are up to $5 billion. You are really not charging the issue any more. The directors and no one is really saying anything publicly about the autonomy that is being taken away. And that is disturbing to me.

You have got an exciting thing like this cancer therapy for children, and we are not moving on it. Boy, back a few years ago, they would have moved immediately.

BY-PASS BUDGET

Doctor, what was your NCI bypass budget request?

Dr. **DeVita**. $1,570,000,000.

Mr. **Early**. And what was your professional judgment of it?

Dr. **DeVita**. $1,463,191,000, is what we submitted to NIH.

AIDS

Mr. **Early**. Doctor, somewhere in your remarks you suggested that there might not be enough money to spend effectively, and I heard Dr. Fischinger suggest it to Mr. Conte. Are you people really concerned about AIDS? Is it a threat that could be equal to the bubonic plague?

Dr. **DeVita**. Well, my own personal opinion is that it does not seem to have the propensity to spread as fast as the plague did.

Mr. **Early**. Can you tell us how many Americans have it today?

Dr. **DeVita**. Well, we think that about a million people may have evidence of the virus but not AIDS. Right around now about 18,000 people in this country have the AIDS——

Mr. **Early**. Probably spreading more than any other?

Dr. **DeVita**. Beg your pardon?

Mr. **Early**. Probably spreading faster than most previous diseases?

Dr. **DeVita**. It is spreading within the high-risk populations relatively fast. While the number of people outside of the high-risk populations have increased in the past year, percentage-wise they have not changed very much. We know it can spread heterosexually, but it has not done so in great degrees.

Mr. **Early**. Oh, you say high-risk because it has been just in the homosexual community in the United States, but the other western countries have shown it in its heterosexual population.

Dr. **DeVita**. Yes.

Mr. **Early**. Does that not scare you?

Dr. **DeVita**. It scares me, yes, indeed.

RESCISSION FOR AIDS

Mr. **Early**. How can you approve a rescission in your department for AIDS? Is it, Dr. Fischinger, that you cannot get the money out?

Dr. **DeVita**. The rescission for the Cancer Institute was restored at the NIH level, so that our level did not change for AIDS.

Mr. **Early**. At NCI——

Dr. **DeVita**. At the NIH level. The money that was in the NCI AIDS budget was restored at the NIH level. It was taken out of the NCI budget.

Mr. **Early**. Well, what I think this Committee intended to do with how we funded AIDS is another perfect example of OMB taking away flexibility, and I think it is wrong.

You said to Mr. Conte that you will have a vaccine in three years. Is that an acceptable time to you, Doctor?

Dr. **DeVita**. When we announced the discovery of the virus in May of 1984, I said that we thought we would have a vaccine to test within three years. And as Dr. Fischinger said, we have the material that produces neutralizing antibodies so that it is possible to have one to test. We have no way of knowing the exact time frame or whether these antibodies will actually work in the human population for sure, but because of the technology we have lots of products to test.

Mr. **Early**. There are so many undiscovered products. This Committee suggested to you last year that on AIDS we wanted the money for discovery; we wanted it for a vaccine; we wanted it for education. NIH overall rescinds some of the money. I have to assume they could not get the money out. If that is not a priority and Star Wars is a priority, my goodness, I cannot believe the directors are not arguing as vehemently as they should be, Dr. DeVita.

I am coming up to my ten minutes. These reductions that you are making, Doctor, stand against everything that you have told this Committee over the years. We are going back on a rollercoaster with NIH. You are making cuts in clinical trials, cuts in research grants, cuts in everything, and you say it is just a little so we can afford it.

I was very impressed with Dr. Bowen when he appeared, Doctor, since he has only been on board 90 days. And I think he is the last hope you've got because the directors are not doing it, in my opinion—with OMB taking over.

Thank you, Mr. Chairman.

Mr. **Natcher**. Yes.

Mr. O'Brien.

Mr. **O'Brien**. Thank you, Mr. Chairman.

As one looks at the voluminous record of the NCI for the last six years, Doctor, your brief but eloquent remarks make one aware that much of it is newly found materials must be attributed to the performance of its Director.

Dr. **DeVita**. Thank you, Mr. O'Brien.

Mr. **O'Brien**. We believe in you.

I have a number of questions that I would like to touch on, and I base it on just a recent experience, firsthand, when I was at the Institutes.

NIH CLINICAL CENTER—BED OCCUPANCY

The question I would like to ask you is: Is it not true that the clinical center simply does not have its beds fully occupied? How do you account for that?

Dr. **DeVita**. It varies by the institutes. Our beds tend to be fully occupied, or our census tends to be higher because of the kind of patients that we get in, especially, for example, with the recent studies by Dr. Rosenberg; they brought an influx of a lot of patients.

So other institutes sometimes have a lower census than we do. In the aggregate, I think the census is about 65 or 70 percent full.

Mr. O'BRIEN. Would you prefer to have that percentage higher?

Dr. DEVITA. My roots come from the clinical center, and I always like to keep the beds full, yes.

There are lots of things to test, and the clinical center is a marvelous place. I have to confess an unabashed bias toward the clinical center. I do not think there is any other place like it in the whole world. You cannot do things like some of the things I have mentioned anywhere else except at a place like the clinical center.

NURSES

Mr. O'BRIEN. It seemed to me in my experience at your center, among others out there, that we are getting a lot for our money's worth. Let me take an example. I thought nursing care was excellent, although I do believe that the nurses generally were getting something less than what is par for the course in earnings out in the private sector. I think the nurses back at St. Joseph's Hospital in Joliet are doing better than the nurses out there in your center.

Dr. DEVITA. Yes.

Mr. O'BRIEN. So it is phenomenal that you can keep such a high quality with that kind of competition, and that says something very good about your staff.

I would wonder if we could do something with respect to the business of staffing NCI or NIAID or the others more generously with nursing care. Does that get back to the dollars and cents problem?

Dr. DEVITA. Well, it always gets back to dollars and cents. I would hasten to add that I am always willing to respond to these kinds of questions, but my opinion is not necessarily the unanimous opinion of the NIH. When we have our internal discussions within our institutes, some institutes would rather have fewer beds and more labs, and other institutes would rather have more beds and fewer labs. It is always a tradeoff in terms of where you put your positions.

My own personal feeling, and this is reflected in the Cancer Institute's distribution of resources, is that the clinical service is such an important part of our operation that we always give it a very high priority. That is how we got the LAK cell IL-2 project going. That is how we discovered lots of other things. That is how this molecular characterization actually began because we always give the clinical center priority.

It would be a better question for Dr. Malone to answer in the aggregate for the NIH, because it is a matter of allocation of resources for beds versus other things.

Mr. O'BRIEN. Dr. Malone, do you have a comment?

Dr. MALONE. I could only, Mr. O'Brien, second what Dr. Wyngaarden said to you yesterday, and that is that full utilization of all of the beds in the clinical center would probably overstress the support services, nurses and everything else at the clinical center, and that somewhere in the neighborhood of a bed occupancy of 70 to 75 percent is probably in the aggregate an achievable, reasonable goal for the NIH as a whole.

And I would finally underscore the point made by Dr. DeVita that there is a wide variation in utilization of beds according to the programmatic sessions of each institute director and the type of research carried on in each institute.

Dr. **DeVita**. I might add one caveat to that Mr. O'Brien. The clinical center is unique, I believe. There is just no other place like it.

Mr. **O'Brien**. When you say the clinical center, do you mean the clinical center for the whole shebang?

Dr. **DeVita**. That is right. The whole hospital.

And then some institutes do unique research and purposely will, for example, use one patient in a two-bed room. So that it looks like they are not occupying their full complement of beds, but the research requires that that patient be isolated in a single room.

So sometimes the low census is just a reflection of the unique characteristics of the clinical center and not just the fact that we do not have enough staff to open up all the beds.

It does not happen to be the case with Cancer Institute, because most our research is high volume research that requires more admissions and more beds. But I really would not like my comments to reflect negatively on the Mental Health Institute where they have to isolate individuals for study more than we do.

One of our problems at the clinical center in general is we are not inventive enough with our census. When a bed is deactivated for purposes of science rather than an inability to staff it, we should deactivate it in the denominator so that our census is more reflective of the kind of institution we are. I do not believe we have done enough of that sort of thing.

Mr. **O'Brien**. Would the National Institutes of Health function better if we were able to provide you with more nurses of the caliber that is required out there?

Dr. **DeVita**. Well, we are functioning well at the level for the research that we are doing. It would be a matter of whether we could start other things and do them well.

BED OCCUPANCY

Mr. **O'Brien**. I guess I keep getting back to the old concern I have over empty beds. You have explained it rather well, but it seems to me there are probably numbers of people out there who would like very much to be referred to the institutes to get the care that each director might be able to apply to it.

And I worry in a sort of a tunnel vision way, not quite with the comparisons that Mr. Early makes, but I worry that we are not paying enough attention to adequate staffing of highly skilled people.

I was impressed by my experience, and I would like to contribute something. I do not know that I have any further comments to make, but if there were something that you would suggest to me that I could do to help you or the other institute directors, what would you say?

Dr. **DeVita**. Well, you have done quite a lot already. I thank you for your very kind comments and appreciate them.

Your view is true of most people who have had some experience with the clinical center. A debate has gone on for decades at the NIH as to whether you should put more or less resources in that component of our intramural program, you have just joined up on my side. I appreciate that.

Mr. **O'Brien**. Thank you, Doctor. Thank you, Mr. Chairman.

SURVIVAL STATISTICS

Mr. **Natcher**. Dr. DeVita, you have statistics on cancer survival rates. As you know, they have often been challenged. How much confidence do you have in your statistics and what do you say to those who question them, Dr. DeVita?

Dr. **DeVita**. They are the best in the world, Mr. Natcher, and the critics would not have anything to criticize if we did not produce them. So in a sense, every year we turn out this lovely blue book that has incidence, mortality and survival for every cancer going back a decade to 1973 when the SEER program was started.

I guess the mistake we made when we first started doing this is that we would only comment on what appeared to be behind the statistics for a few of the cancers. And when we did not comment on one cancer, other people made assumptions about what we thought. The one that has been used the most, I guess, is prostate cancer by Dr. Bailar. When we did not comment on the increase in incidence and the increase in survival rate for prostate cancer, he assumed we were attributing this to more effective treatment. And so he criticized us for claiming success in treatment of prostate cancer on the basis of SEER date, which we were not doing at all. His interpretation that we are diagnosing some cases earlier and, therefore, seeing a rising incidence and a rising survival is probably correct. The answer is that the data base is unmatched in quality around the world, and it gets increasingly important as we go along because it is our monitor. It is the way we can see how close we are going to come to the goals that we set for the year 2000 a few years ago.

I am very pleased with them, and we accept the criticism. In fact, we had a seminar at the National Cancer Advisory Board on the statistics, at which we invited Dr. John Cairns as a speaker because he also has been a critic of those statistics. I think it went very well. We were rather pleased with the outcome.

Mr. **Natcher**. Doctor, a few questions. You will recall I said to you when you get the transcript back, you go into detail pretty much.

My next question otherwise would have been briefly, "what evidence is there that we are winning the war on cancer?"

So when you get the transcript back, go into detail pretty much, with us, if you would please.

[The information follows:]

WINNING THE WAR ON CANCER

The evidence lies in our national mortality statistics, in the data collected by the NCI to track cancer incidence and survival, in the results from recent clinical trials, and in the exciting new findings on the etiology of cancer now emerging from the Nation's research laboratories.

Cancer is a disease that may develop over many decades; when it does strike, many years are generally necessary to determine that a patient is truly free of cancer. Often the percentage of patients who survive five years is used as a surrogate for the likelihood that a patient will be cured of cancer, although we know that for some cancer sites, such as breast cancer or prostate cancer, a longer follow-up time is generally necessary to assess the patient's full prognosis. Therefore, to accurately assess trends in cancer, it is best to take a broad longitudinal view of cancer indicators.

For instance, the most accurate indicator available for assessment of long-term trends, for a period of 30 years, is the mortality rate from cancer. We use the age-adjusted mortality rate to account for the aging of the population. (Since the incidence of cancer increases with age, the assessment of trends is confounded by the fact that our population is aging; therefore, we would expect to have an increase in the number of cancer cases with an aging population, even with the possibility of advances in prevention, screening and treatment. The age-adjustment process effects the necessary normalization so that trends over time may be accurately discerned.)

Over the last 30 years the cancer mortality -- not including lung cancer -- has fallen by 13.4 percent, from a rate of 144.0 in 1950 to a rate of 124.7 in 1983, equivalent to 47,000 fewer deaths each year. Mortality from lung cancer, by way of contrast, has increased from a rate of 21.6 per 100,000 males in 1950 to 72.9 in 1983; similarly, the rates in women have increased from 4.8 to 24.3 over the same time period. We exclude lung cancer from the total cancer figures because its primary cause, cigarette smoking, is well-known and the increase in mortality from this disease is directly due to the increase in smoking over the first 60 years of this century. That picture has changed, however, since the publication of the Surgeon General's Report on Smoking and Health in 1964. Indeed, over the last 20 years, smoking has fallen in males from 52 percent of adult males smoking in 1965 to 32 percent in 1983, a decrease of one-third. And, as a consequence, lung cancer incidence in males has decreased from 1982 to 1983, the first such decrease in over 50 years. The picture for women is not as positive since their smoking prevalence has fallen only by 14 percent over the same time period.

The decrease in mortality cannot be directly compared with changes in incidence over the same time period since such data has only been collected in a systematic, ongoing basis since 1973 by the National Cancer Institute's SEER (Surveillance, Epidemiology and End Results) program. However, a similar decline in mortality over the 30-year time period is also seen in the SEER data. The

10-year SEER data also shows a relatively constant age-adjusted incidence rate -- not including lung cancer. Constant incidence and falling mortality are most consistent with the effects of improved cancer treatment. The evidence for improved treatment over the last 15 years is quite clear for a number of cancer sites. Hodgkin's Disease, childhood leukemia, and a number of other cancer sites have been shown to be highly responsive to particular treatment regimens, both in the laboratory and in clinical trials. The transfer of this treatment technology into the general medical community during the 1970s has resulted in the following decreases in cancer mortality in the United States: Hodgkin's Disease, 40 percent; childhood leukemia, 36 percent; testicular cancer, 52 percent - all since 1973. A more short-term measure of progress -- cancer survival, measured as five-year relative survival -- has also shown improvement for many sites. Breast cancer relative survival has increased from 72 percent for patients diagnosed in 1973 to 75 percent for patients diagnosed in 1978, the latest year for which we have five-year survival statistics. Colorectal cancer survival has gone from 46 percent to 52 percent, and bladder cancer survival has increased from 72 percent to 77 percent.

Progress has also been made in cancer screening. Breast cancer, second only to lung cancer as a cause of death in women, and three times as prevalent as lung cancer, can be detected easily through physical exam and mammography. The clinical studies and a demonstration program have proven this fact, and a concerted cancer control effort is underway to encourage such screening, particularly among high-risk populations. Clinical studies showed that at least a 30 percent reduction in breast cancer mortality attributable to screening is possible. Cervical cancer can also be detected early through screening, and such screening has been largely responsible for the 36 percent drop in cervical cancer mortality since 1973.

Additional evidence of progress against cancer can be found in the cancer control effort which has been considerably strengthened in the areas of smoking, diet and screening and the research on cancer prevention. New communications channels for cancer information for both the public and medical professionals are being identified and explored, such as the Physicians Data Query (PDQ) system, an on-line interactive computerized system designed to bring state-of-the-art treatment information to the Nation's physicians and their patients. In addition, the Cancer Information Service continues (1-800-4-CANCER) as a well-recognized information channel with some 400,000 calls received yearly from around the country. The Community Clinical Oncology Program (CCOPs) has been developed to bring the benefits of clinical trials participation to communities across the country. In all these ways, new channels for transferring state-of-the-art cancer information are being opened, and it is through these channels that change will continue to be effected.

Certainly the exciting new knowledge of how cancer develops and how the cancer cell behaves poses the greatest hope in continued progress against cancer. This new knowledge is leading to new ways to prevent cancer, to reverse the cancer process early in its development, to use the body's own immune system to protect against cancer, to improve treatment techniques, and to find new ways to block the process of cancer metastasis.

All these facets of cancer research, from its statistical trends to basic knowledge, support our growing confidence that the cancer toll has been reduced and that progress will continue.

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LAK THERAPY

Mr. **Natcher**. Recently, as you know, there was a great deal of publicity in the national news media about Dr. Rosenberg's research with cancer patients at NIH using a new drug.

If you will Doctor, give a brief report on the status of this research. And, of course, when you get the transcript back, you may want to go into detail a little more. What about this Doctor?

Dr. **DeVita**. Well, I counted, at the end of last week, total of 71 patients being treated so far. He reported 25 in the New England Journal of Medicine. These are 71 completed. We have another dozen or so that are just through and not yet evaluable. And, of the 71, we have about 40 percent overall response rate: one hundred percent in kidney cancer, fifty percent in melanoma and 30 percent in colon and only one lung cancer treated and one lung cancer responding.

I believe the most remarkable feature of this study are the responses in kidney cancer. We have seen some very dramatic results in people with widespread kidney cancer of the kind that are very likely to provide significant impact on this disease.

I would not be at all surprised, when we move to the next step, which is to apply this therapy in patients with kidney cancer, whose tumor has been removed surgically, but have a high risk of recurrence, that we see a major impact on mortality statistics from kidney cancer in a big hurry.

Mr. **Natcher**. I understand that the publicity given to this research produced a flood of inquiries from desperate cancer patients who could not possibly be included in an experimental project of this nature. Dr. DeVita, is it not cruel to publicize such experiments, when the treatment can be made available only to a privileged few?

Dr. **DeVita**. Well, you know, I do not know how to deal in a public organization without having this kind of thing happen. We watched on a day-by-day basis the progress of Dr. Rosenberg's work.

The question we asked ourselves is: when do we publish it? It was presented before the National Cancer Advisory Board, the President's Cancer Panel and other places, and scientists began to hear about it—the early criticism we were receiving was: why not publish it so we can see the data?

So, when we hit 25 cases, with 40 percent response, some of which were complete remissions, we decided the time had come to publish it.

Obviously, scientists like to publish their work in good journals such as the New England Journal of Medicine. We held no news conference, we just submitted it for publication, and it was published. But since it is monitored by the public press, they picked it up and made big stories out of it and, that is what happened. We had a thousand calls a day for a period of a week or so, from patients who wanted to go into therapy.

As Dr. Rosenberg pointed out in subsequent news interviews, for most patients it was not the therapy for them. It is not easy to take at the present time. And for some patients, it just is not appropriate to give this kind of therapy.

I do not know how to avoid getting that kind of attention. If we do not publish, people say you are hiding something. If we do publish it, and it is exciting, it gets this kind of publicity because, we are a very open institute and a very open country.

Mr. Early. Did you tell any of those thousand calls that you could not do it because you did not have the money?

Dr. DeVita. No, I do not think we did Mr Early.

PATIENT SELECTION

Mr. Natcher. Now Doctor, how do you select patients for inclusion in such experiment? How is this done, Doctor?

Dr. DeVita. The fairest measure that we have been able to use is that we handle about eight patients a month on this protocol and if an appropriate patient calls when there is a vacancy, or the doctor for that patient calls when there is a vacancy, we take the patient. We have no waiting list because, with patients with advanced cancer, you cannot have a waiting list. So that it is just a matter of calling us at the time when we have a vacancy, if you have the right kind of cancer.

At the moment we are focusing on kidney cancer, melanoma, and colon cancer. If you called with other kinds of cancers we would have said to those patients, Mr Early, that we are not using that protocol for that cancer at the present time. We have expanded it somewhat since then.

Mr. Natcher. Dr. DeVita, to what extent is Dr. Rosenberg's experiment with interleukin-2 being tried out elsewhere?

Dr. DeVita. We have about ten centers now. Six have just been established—as we speak—I imagine they are putting their first patients on. We started them about a month ago. We wrote letters to all major cancer centers in the country and to the cooperative groups, and asked those who would be willing to use the protocol that Dr. Rosenberg developed to compete. The Cetus Corporation supplied the interleukin-2 free for all these studies—it was very nice of them to do this. They supply a very large amount of material. We now have six of our institutions, dividing up two and a half-million dollars to study 200 to 300 patients in the next year. We have about four more using slightly different variations of the protocol.

Mr. Natcher. Dr. DeVita, if you had additional funds would you use them to expand the experiments with interleukin-2?

Dr. DeVita. Well, we are going to have to expand the experiments with interleukin-2, Mr. Natcher. There is no question about it. I think we have to move into the early stages of kidney cancer situation very quickly. So, yes, of course, we would obviously do that.

INTERFERON AND TUMOR NECROSIS FACTOR

Mr. Natcher. Tell us briefly, if you will, about the latest research findings, Doctor, with respect first to, (a) interferon and (b) tumor necrosis factor (TNF)? What about that, Doctor?

Dr. DeVita. Well, interferon is interesting. This Committee goes back a long way with interferon, to about 1979 I believe. At that time we had nothing but crude interferon; one one-thousandth of a part of the material we were using was interferon. Very shortly after 1981, we had pure interferon and it has gone through a number of tests.

It turns out to be the treatment of choice for an uncommon tumor, called Hairy Cell leukemia. It works in chronic myelocytic leukemia and has some modest effect in kidney cancer and some kinds of lymphomas. It looks like it is going to fit in—using it with other materials, other biologicals. So the pure recombinant DNA version is under going evaluation. It has clearly found a place in the therapeutic armamentorium, but not as much of a place as some people had hoped back in 1979. Tumor necrosis factor (TNF) is brand new biological in one sense. We have known it was there for about two decades. But, you could not do anything with it because we had it in such small quantities. Then, like other materials, the gene was cloned and we had buckets full of the material. There are about five critical trials going on with tumor necrosis factor at the present time. Results really are too early for comment. By the time I come back next year, we should have a better idea as to whether or not it is going to impact cancer activities.

CANCER LEGISLATION

Mr. NATCHER. Legislation to extend the authorizations in the National Cancer Institute was finally enacted into law as you know, after the President had vetoed the Bill, I believe, twice. Doctor, how does this legislation change the way you operate, if any? Is this good legislation? You know Doctor, at the time, I had my doubts about some of this, what about this Doctor?

Dr. DEVITA. Well, I believe the President vetoed the Bill for a variety of reasons, Mr. Natcher. Not necessarily just because it was the re-authorization of the Cancer Act. But, personally, the Cancer Act has always been very useful at the Institute. It does give us more flexibility in terms of how we manage our day-to-day business. Especially how we set up our advisory committees and how we can train people. Initially through this Committee, it was the source of the cancer expert positions that have been so valuable to the NIH in general, so it has been a very valuable tool for us.

FTE CEILING

Mr. NATCHER. Do you have FTE ceilings for 1986 and 1987? If so, what are they?

Dr. DEVITA. Fiscal year 1987 is 2,072. It will be the same as the 1986.

Mr. NATCHER. Doctor, can you give us the ceilings for 1984 and 1985?

Dr. DEVITA. In FY 1984, we used 2,416 FTE's. For FY 1985, we used 2,230 FTE's. We dropped 344 FTE's since 1984.

Mr. NATCHER. What effect are employment ceilings having on the operation of your institute?

Dr. DEVITA. Well, we have had to reorder our position priorities and not restaff certain areas and allocate resources to the programs I have been talking about and make some other laboratories smaller.

Mr. **Natcher**. To what extent Doctor are employment ceilings restricting your ability to conduct intramural research?

Dr. **DeVita**. It makes it more difficult, Mr. Natcher. I would be less than candid if I said we could run at the same speed. We have to run a smaller organization, rather than a large organization at a slower speed. That is my preference. I would rather reduce certain areas and let others go. Dr. Rosenberg's positions have increased during the time of the reduction because he needed them to do his work. So, it requires that you make harder choices about what you support.

RECRUITMENT OF NURSES

Mr. **Natcher**. Are you having difficulty at this time, Doctor, in recruiting and retaining nurses in the Clinical Center?

Dr. **DeVita**. The nurses in the Clinical Center are not under the Cancer Institute. They are the responsibility of the Clinical Center Director and the Director of NIH. Perhaps Dr. Malone might answer that one.

Mr. **Natcher**. What about it, Doctor?

Dr. **Malone**. Yes, Mr. Chairman. The recruitment of nurses is a perennial problem with the Clinical Center. The Director is always in the process of trying to attract the best nurses. And, I would say that at the present time, despite this difficulty, that we have a staff that is able to carry-on the current programs of the various institutes.

CONDITION OF NIH

Mr. **Natcher**. Dr. Malone, how long have you been out at NIH?

Dr. **Malone**. I am nearing a quarter of a century, Mr. Chairman.

Mr. **Natcher**. Do you feel better today than the day you first started out there, Doctor?

Dr. **Malone**. Are you talking about my own physical condition?

Mr. **Natcher**. No, Doctor I am talking about NIH generally.

Dr. **Malone**. Mr. Chairman, I feel exceedingly good about the National Institutes of Health. I have observed, as many of my colleagues, the simply spectacular developments which have been occurring throughout the NIH and we see this knowledge increasing, escalating every day. And, as a result of it, I think that we will see, by the year 2000, many cures and I think that the practice of medicine will be decidedly different as a result of what has been stimulated by NIH, by our own scientists and by the work that has been supported throughout this country and abroad.

Mr. **Natcher**. Thank you Doctor. Mr. Conte, I yield to you.

BREAST CANCER

Mr. **Conte**. Well, I have more questions on AIDS Doctor and I will put 10, 11, 12, and 13 in the record for you to answer later. Doctor, from your previous appearances before this Subcommittee we have come to learn that many cancers, if detected early enough, are curable. One of those, breast cancer, has benefited a great deal in recent years from new techniques and technologies. What is the present survival rate for breast cancer?

Dr. DeVita. Overall, about 50 percent of all patients with breast cancer survive without recurrence. It depends a lot on stage. Early stage breast cancer is about 85 percent curable. One can detect breast cancer earlier with the state of the art at the present time. If mammography were used fairly routinely, in women beyond the age of 50, we think you could effect a 30 percent reduction in mortality from breast cancer.

Mr. Conte. Last year, the Institute had a huge cancer screening program for breast cancer. Do you have any estimates how many women make use of the techniques that are out there? It would seem to me that this would be one form of cancer where we could pretty quickly wipe out the mortality rate.

Dr. DeVita. Well, that program is over. But, it screened some 275,000 women—we followed another 65,000 for other reasons later. In this country, and this is in the realm of the practice of medicine and medical economics, not the Cancer Institute per se, I believe only about 15 percent of women over the age of 50 get routine mammography. There are economic barriers that are complex. Sometimes, it is a matter of acceptance and fear of exposure to radiation. I do think it is an area where the awareness that you can reduce mortality with the current technology, which is quite safe, will help. We clearly think you can reduce mortality.

There are studies now in this country and in Canada and abroad that show that you can reduce mortality with routine mammography over the age of 50 by detecting the cancer earlier.

Mr. Conte. You say economics. Is it the cost?

Dr. DeVita. Yes. In many places, a mammogram costs about $200. Many third party carriers do not cover mammography for screening purposes. There are some places that are experimenting with units that do high volume mammography at cost—somewhere in the range of $30 a mammogram. We are looking for more people to get into this and make it routinely available.

It is quite safe now. The excessive fear created some years ago by Dr. Bailar, the same critic of our survival statistics, that you would cause more cancer than you would prevent, is long gone in the medical community. The problem is long gone but, the fear is still there in the American woman, that they are being exposed to radiation and they are going to get cancer from mammography. The fact of the matter is that for women over the age of 50 with the current technology, it is really quite safe.

LUNG CANCER

Mr. Conte. You mentioned this morning that there was a drop in lung cancer for white males. On the whole though, that report was pretty dismal for both women and minorities in this country. Why is the rate for white males falling, while the rate for women and minorities are staying the same?

Dr. DeVita. Well, women have taken up smoking with great gusto. And, the rate of increase of cigarette smoking is well beyond that of men. Mortality had already come down in men under the age of 45 from lung cancer and last year in all white males in the U.S. That is strictly the result of cessation of smoking, sir, because the treatment has not improved for most lung cancer. It is just a matter of more women smoking, they are catching up to men.

There are also more heavy smokers in blue collar workers and more minorities in the blue collar field so that in the black population there is a bigger problem with smoking. We have some special programs in smoking prevention and cessation targeted to women to blue collar workers and minorities to try to get at this core because if we are going to hit our goals for the year 2000, we have to get down to the hard core, heavy smokers and convince 50 percent of them to stop smoking by the year 1990.

Mr. **Conte**. What is your target?

Dr. **DeVita**. Fifty percent reduction in mortality by the year 2000.

Mr. **Conte**. That sounds good. What are you doing, advertising? It is easy to set a target.

Dr. **DeVita**. The SEER program keeps our feet to the fire. When we established those goals—the LAK cell project had not reached maturity, the positive studies that I talked about last year were not there. If all those studies stayed positive, on the treatment side, of the 175,000 lives we would have to affect by treatment on our list, we already have potential impact of 126,000, and so we are not doing too badly.

COLON CANCER

Mr. **Conte**. The President's recent bout with colon cancer has drawn a lot of attention to the disease. How prevalent is colon cancer in America?

Dr. **DeVita**. About 140,000 case a year in this country. In the aggregate, it is the commonest cancer when you put male and females together. There are sixty thousand deaths a year from colon cancer.

Mr. **Conte**. It can be treated though, if detected early?

Dr. **DeVita**. About 40 percent of people are cured just with surgery alone, depending again, on how early it is. For the rest, we have very high hopes. One of the studies I referred to earlier is a positive adjuvant study. The patient has surgery, but, we know they are at high risk of recurrence and there is a program that was developed at the Mayo Clinic which is being re-tested nationally now, which shows that you can improve survival and decrease mortality by using this adjuvant therapy. We are also going to put the LAK cell program into the adjuvant situation in colon cancer.

Mr. **Conte**. Some recent findings that have hit the papers show that calcium may be an effective deterrant to this disease. In fact, foods that are high in calcium are now making a lot out of these findings What are your thoughts on calcium as an effect means to cut the risk of colon cancer? Would it be equally effective for both men and women?

Dr. **DeVita**. I cannot answer the latter part. The data on calcium effect are very interesting and we are persuing this question. It may fall under the umbrella of fat in the sense that one of the influences of fat may be to precipitate calcium as a soap like material. One of the many things that fat could be doing would be taking calcium out of the bowel when it might be protective. We are looking at that, although we are not making any recommendations at all about calcium intake other than what has already been made for post-menopausal women. There are some recommendations for post-menopausal women to supplement their diets with calcium as a result of a consensus development conference on osteoporosis at the NIH.

FORMALDEHYDE

Mr. CONTE. Doctor, your Institute recently came out with a report that has probably set back the hands of time in terms of the risks generally associated with the chemical formaldehyde. Can you tell us a little about that report and how it differs from the general impression of the hazard posed by formaldehyde?

Dr. DEVITA. That's a very interesting study. It is also a very good study. We're very proud of it. It was started in 1981. It took us about four years to complete it, and it includes 26,000 people. I do not think anybody could do another study that would provide better results.

This study does not negate the fact that if you expose animals to high enough levels of formaldehyde, they get nasal cancer so that in animals formaldehyde is a carcinogen.

All it shows is that for the level of exposure of these 26,000 workers, over the time frame of this study, under the circumstances described, formaldehyde does not appear to be a carcinogenic hazard. This is actually good news.

That does not mean if you double the exposure to formaldehyde that the news would stay the same.

Under the terms of those studies with the level of exposure and duration of exposure it does not appear to be a hazard. Since ten different plants were used as the data base, it gives something like ten different studies. This gives a lot of strength because the consistency across the ten plants was fairly uniform.

Mr. CONTE. If I recall correctly, the report found a 32 percent excess of lung cancer deaths and higher than expected rates of upper respiratory cancer. Are not those figures alarming?

Dr. DEVITA. Well, overall there were less cancer deaths than expected, and in lung cancer, they were slightly higher than expected. Brain cancer and leukemia, two cancers that have been associated with formaldehyde in the past were lower than expected. So there was some variance around that.

Then what epidemiologists do is to look at the exposure time because a basic tenent of epidemiologic studies like this is that if there is a relationship between an excess rate and the material under study then with time you should see a greater excess in those that are being exposed longer, and this did not show up.

Given the minimal differences and the fact that it was not related to time and dose, they do not feel it is significant, but they are exploring one subset of cancers, nasopharyngial. That is not the same as a nasal carcinoma, but it is the back of the pharyn and is an unusual cancer. Eight cases were found and two were expected, and they have to examine that a little bit further. But generally speaking, given the fact that we are exposed to 500th hundredths of a part per million, say, in our homes as a result of insulation and other things of that sort, which is rather low, that level of exposure certainly should not be harmful according to these data.

Mr. **Conte**. I read somewhere the other day that you may cause more damage by ripping out the walls and sending all the particles into the atmosphere, and that maybe it is better to just leave it sealed up.

Dr. **DeVita**. Urea formaldehyde is used as an insulator, and in homes where urea formaldehyde is used, the exposure rate is about one 500th of a part per million.

I am not 100 percent certain on this final point but I think the data on nasal pharyngial cancer is at exposure rates of well over 3 parts per million. So you are talking about quite a difference in terms of dose. I do not know the difference between ripping it out and leaving it in.

Mr. **Conte**. It just agitates the problem.

I thank you, Mr. Chairman.

Mr. **Natcher**. Mr. Early.

GRANT FUNDING

Mr. **Early**. Dr. DeVita, under the current proposal there are 924 grants funded. Under the Administration revised 1986 proposal, the NCI would fund only 850 or 74 fewer. For the record provide what areas of research would be affected by this reduction, and tell me, do you think that is progress?

Dr. **DeVita**. Well, in the context of having to restrain resources, Mr. Early, we will try to fund the highest priority programs.

Mr. **Early**. But when you say to fund the highest priorities, Doctor, to Mr. Natcher, you said interferon was being used for something that we did not expect them to be used for when we first started.

I think you said with regards to molecular characterization cancer therapy that a pediatrician discovered that? I mean, you knock off the programs that you do not think are as good as the others, that is not progress. That is retreat.

Dr. **DeVita**. Well, Mr. Early I do not like to measure progress in terms of numbers of grants because I think that is only one parameter to use to measure progress.

Mr. **Early**. No, but we can only measure potential by what we fund. I mean, it is as simple as that. Our business is dollars. This Committee has never suggested that NCI or any of the Institutes or NIH do not retain total flexibility. That is why you have the interferon for some other use and you have a pediatrician.

That is why I was really surprised at Dr. Malone. He evidently does not suspect that the flexibility is decreasing, I have not talked to anyone else that does not think that their flexibility is diminishing.

As Mr. Miller—I guess we should call him Dr. Miller. He knows more about cancer than you do. He knows more about heart, lung and blood than Dr. Lenfant. He is going to tell us what the potential is?

You are going to fund 143 less new and competing grants than in 1985, is that true, Doctor?

Dr. DeVita. Yes, that is probably the number for 1985. Yes, we had 1,017 in 1985.

Mr. Early. 143 less than 1985.

Dr. DeVita. In competing grants, yes.

Mr. Early. What is NCI's pay line under the 1986 revised request and under the 1987 budget request?

Dr. DeVita. About 160.

Mr. Early. 160. And what will it be for 1987?

Dr. DeVita. 160.

Mr. Early. 160. Isn't that wonderful.

What was your pay line in 1985, Dr. DeVita?

Dr. DeVita. It is 173 and 36 percent funded.

Mr. Early. That is the whole point of science. If we were ever to just take the priorities, say, we would just take the ones that were going to be productive—but we have to fund a whole lot to find out a little bit.

What percentage of approved grants would be funded under 1986 revised and the 1987 budget request?

Dr. DeVita. 27 percent.

Mr. Early. 27 percent. Are you comfortable rejecting 73 percent of the requests, Doctor?

Dr. DeVita. Well, there has never been a time when we funded all approved applications.

Mr. Early. No. I think 20 years ago we funded over 80 percent of approved science that we got.

Dr. DeVita. I was too young to remember. [Laughter.]

[The following was provided for the record:]

Grant Support Level

The FY 1986 appropriation level, after the comparable transfer of AIDS activity to the Office of the Assistant Secretary for Health, reflects that 924 competing research project grants would be supported. The revised 1986 estimate is that 850 competing research projects would be funded, a reduction of 74 competing grants. It is projected that this reduction would not impact in any one particular research area but it would result in fewer competing applications being supported. Funding decisions would be based on the priority score ranking of the peer-review system and program relevance.

GRANT NEGOTIATIONS

Mr. Early. It is tough. Historically noncompeting grants have been funded at close to the full commitment levels or 99 percent. Why should noncompeting grants be funded at less than the approved levels after review, Doctor?

Dr. DeVita. Well, there is a matter of flexibility in the sense that we are saying that if we have to make sacrifices that we should share the sacrifices between the competing and noncompeting grants.

Even at the reduced amount of 5.0 percent reduction in the noncompeting grants, there is still a slight increase over the prior year. Even with the reductions that we're making in the competing grants, competing renewals are getting increases over their current level since on the average, they are recommended for 30 percent increases.

Mr. Early. I hope you give this dissertation to the 1,000 people that you told us called you. I mean, I hope you did not just say, "Well, no, it is not this or that." I hope you gave them all this. "Oh, no, it is budget restraint. I am sorry you've got cancer. I am sorry your 10-year-old, your 3-year-old got cancer. We cannot do it." That is what they would have done ten years ago, Doctor.

Doctor, the budget justification states that there will be a downward negotiation of close to 7 percent and 6.4 percent in competing and noncompeting grants. Will each grant be reduced the same amounts or will there be an average?

Dr. DeVita. No, it just comes out to be an average.

Mr. Early. I am certainly happy that you are at least doing that, and we are not accepting every grant the same as the other.

Dr. DeVita. No, we negotiate individually with grantees.

CLINICAL COOPERATIVE GROUPS

Mr. Early. That's fine. Doctor, I understand that clinical cooperatives groups are an important part of NCI's research effort. In fact, they are the largest part of your clinical trials program, is that correct?

Dr. DeVita. That is correct. $49 million.

Mr. Early. While the 1987 budget request will support 228 cooperative clinical grants, it is 43 less than 1985, Doctor?

Dr. DeVita. Yes, 228 awards are projected.

CANCER FUNDING—OTHER COUNTRIES

Mr. Early. Are you embarrassed that West Germany and Japan invest more of their money in research? We should probably shift Stockman or Miller over there and let them run their programs.

Dr. DeVita. I do not think they are, Mr. Early. I mean, Japan, which is a very fine research establishment, has just started its own cancer program to the extent of $30 million a year.

One of the reasons they were able to do it at that level was because they are building on the basis of our programs. Where we are stopping, they are taking off.

Mr. Early. If you can, will you, for the record, supply what you think the other countries that are participating are doing in their commitment to research?

Dr. DeVita. I will try but it is hard to estimate because they provide different salary arrangements for their investigators than we do. They are often in a state medical system and we have a different kind of a support service.

Mr. Early. Well, as best you can. You people have all gotten to be excellent statisticians justifying a very unacceptable budget.

CANCER PROGRESS

Doctor, do you think it is a most productive period in history?

Dr. DeVita. I do not think there is any question about it. In our field, I really do think we are going to totally understand the cancer cell and why it becomes malignant. I would be very surprised with that level of understanding that we will not be able to make rather startling impacts of the type we already talked about.

Mr. **Early**. Doctor, this Committee has committed a billion dollars a year. Do you think that was well spent or do you think it was wasted?

Dr. **DeVita**. I am pleased with the way the cancer program has spent its money if you are referring to that billion. We have been at a billion since 1980, and I think we are spending it well.

INTERFERON

Mr. **Early**. Well, is it not progress to want to bring it to fruition as quickly as possible?

Dr. **DeVita**. Yes. There are things that happen, though, Mr. Early, in all fairness. The interferon story is a good one because at the time the first debate over interferon came up, it would have cost $40 million to get enough interferon to treat high risk patients.

Mr. **Early**. Well, that was when it was expensive.

Dr. **DeVita**. Now, it costs nothing to treat thousands of patients because of genetic engineering. So there are offsetting things happening, and part of the technology is making some things cheaper for us. We do not even have to pay for the IL-2.

Mr. **Early**. When interferon was species specific, before it was synthesized, wasn't that something that NIH really helped on?

Dr. **DeVita**. There was a heated debate over whether or not interferon should be tested in its crude form. There was not uniform opinion at the NIH level.

Mr. **Early**. I was always very comfortable when the professionals out at NIH were arguing amongst themselves.

Dr. **DeVita**. Yes, I think it is very healthy.

Mr. **Early**. But very disturbed when you were arguing with OMB.

Dr. **DeVita**. In all fairness to OMB——

Mr. **Early**. Please, I do not want to be fair to them. [Laughter.]

Dr. **DeVita**. Let the record show that I was about to be fair to them. [Laughter.]

AIDS

Mr. **Early**. On AIDS, Doctor, Mr. Conte more or less directed that we have one titular head of it because of the threat. And I think Dr. Bowen said it was Dr. Dowdle that has been appointed.

Dr. **DeVita**. Yes.

Mr. **Early**. Do you report to a Dr. Dowdle your findings or any of your information?

Dr. **DeVita**. Yes.

Dr. **Fischinger**. We have a very regular reporting system. It goes through a series of committees. Dr. Dowdle is apprised from the NIH point of view by myself and Dr. Wyngaarden.

Mr. **Early**. Are you satisfied that you got all the money that you could effectively spend, Doctor? We are not looking to throw money at you to spend it, but to come up with discovery and a vaccine for AIDS?

Dr. **Fischinger**. I would certainly say that this program has been much better treated than a number of other programs. I think if you talk to individual investigators in the area, I think you will find nationwide that the individuals will say that they could do more if they had more resources.

IL-2 AND TUMOR NECROSIS FACTOR

Mr. EARLY. Dr. DeVita, a final question. With the two exciting things the Chairman spoke about, IL-2 and tumor necrosis factor, are you going to have to play one against the other? I mean, are you going to have enough money to develop them as quickly and as they should be developed?

Dr. DEVITA. Well, I cannot answer the question specifically, and I will tell you why. The answer is they are not competing with one another at the present time.

Mr. EARLY. Are they going to compete for the dollars? Are you going to say we've got to put it over into IL-2?

Dr. DEVITA. If we do not make IL-2 LAK cell therapy simpler, it will be expensive to do all the things that we want to do we will be scratchinq our heads trying to find $20 to $30 million.

But we think we have already stumbled on a way to make it simpler so that that is going to change the costs as we go along. So any answer I give you is not likely to be terribly accurate except that at the moment if we have to take Dr. Rosenberg's study and expand it to 1,000 patients, it would cost what I said.

If we are able to get rid of the side effects, it will require much less in the way of care. We hope it will become much cheaper and go through the same sort of phase inteferon went through—crude, expensive, refined, cheap.

The answer is I hope they do not compete because they are both exciting.

Mr. EARLY. Thank you, Mr. Chairman.

Mr. NATCHER. Mr. O'Brien.

Mr. O'BRIEN. Thank you, Mr. Chairman.

PROMISING BREAKTHROUGH

Dr. DeVita, your comments with respect to the exciting things that are happening around us and with respect to your Institute particularly leads me to ask the question: Is there any one line of research including all aspects of immunology, nutrition, cause and prevention, detection, diagnosis that seems to hold at this moment the most promise for breakthroughs in the ending of this cancer scourge?

Dr. DEVITA. That will get me in a lot of trouble with my colleagues, but I will pick one. I think that the field that is the most exciting at the moment is molecular biology.

We support about $241 million worth of research in molecular biology, and we are very pleased with the end result.

Prevention of chemical carcinogenesis, the biochemistry of drug resistance, all these things are so closely related to it that it is very hard to make a distinction.

SUPERCOMPUTER

Mr. O'BRIEN. Last year, I think you suggested in your testimony that staff changes at the laboratory for mathematical biology at the Frederick Cancer Research Facility had provided for the recruitment of a new chief whose main task was the application of a super computer to cancer research.

Can you expand on those changes and has such a machine been made available for the NCI?

Dr. **DeVita**. As we speak it is purring away. It is up and running, and Dr. Jake Maizel, who came over to us from the Child Health Institute, is chief in that laboratory at Frederick.

The machine was installed, I believe, in February or early this month, and it is operational at this minute. We are very excited about it because to do things like mapping the entire human genome you need the kind of computing power that only the very, very high speed so-called super computers provide.

The one we have up there is a Cray X-MP.

PAIN AND CANCER

Mr. **O'Brien**. One last question that is more common, I guess. When I was at the NIH and they were dealing with my disk problem, I happened to meet a doctor named Angela Miser, who seems to have the extraordinary specialty of dealing with pain of children with cancer.

Is that a different slant to NCI's approach to cancer problems?

Dr. **DeVita**. Well, about 20 percent of cancer patients get rather severe pain. For adults, we have a pain team at the clinical center that examines individual situations to try to make sure patients get the best possible medication.

Dr. Miser is working in the pediatric field, and the problems of determining pain and relieving pain in children are some what more difficult because children do not express themselves the same way that adults do.

So her work is a little bit different. She has been using patch application of pain medications to help relieve pain.

Mr. **O'Brien**. Is there something we could do for Dr. Miser?

Dr. **DeVita**. She is planning on leaving the Institution, but I am not 100 percent sure at the moment, Mr. O'Brien. I will have to check.

Mr. **O'Brien**. Would you supply that for the record.

Dr. **DeVita**. Certainly.

Mr. **O'Brien**. Thank you, Doctor.

Thank you, Mr. Chairman.

[The information follows:]

Dr. Angela Miser

For the past three years, the Pediatric Branch's studies on the management of pain have been coordinated by Dr. Angela Miser, a part-time member of the Pediatric Branch.

Dr. Miser's appointment in the Division of Cancer Treatment was extended for six months in January of 1986. While Dr. Miser's work is important, there are other high priority needs, such as the LAK plus IL-2 study, which command a significant shift of resources and promise to benefit a large number of patients.

The current plan is to have Dr. Miser serve as a Guest Researcher after her appointment expires.

CANCER TREATMEN

Mr. **Natcher**. Dr. DeVita, how much controversy is there in the medical profession as to the most effective methods for treatment of cancer? Just generally what would you say, Doctor?

Dr. DeVita. The answer is there is a great deal of controversy. The whole cancer treatment field is a halfway technology that is evolving very fast. Since we grew up as specialists, surgeons, radiotherapists, medical oncologists who give chemotherapy, other oncologists, every specialty is being pulled and tugged in different directions.

I find it healthy, much as Mr. Early said. We argue amongst ourselves about who should be doing what and how much better and that is a healthy sign of an evolving field.

Mr. Natcher. In your view, how serious is the problem of the physician who is treating cancer patients without being familiar with the most recent developments in cancer treatment?

Dr. DeVita. I believe that is a serious problem. I have given a few lectures recently on the subject, because it is a serious problem. That is, if you are unfamiliar, with giving these therapies you tend to make modifications in the treatment in such a way as to make it easier to deliver and produce less side effects for the patient.

But as a result, you often abrogate the curative effect. For example, with chemotherapy, if you reduce the doses by half because patients get sick, you often will lose the ability to cure the patient entirely.

My view is if you tell a patient that, they'll say, "I would like to have the full doses, please." Patients are not necessarily fully informed. So it's a problem that has grown up out of the rapid growth of the field of medical oncology. It will be addressed by the American Society of Clinical Oncology in a patterns of care study to see how chemotherapy is delivered.

Mr. Hatcher. How widespread is the problem of failure to diagnose cancer early enough?

Dr. DeVita. The issue that we were discussing earlier with breast cancer is a good example. There could be a 30 percent reduction of mortality if everybody would routinely use mammography over the age of 50, that means 9,000 women a year in this country would not necessarily die if mammography was routinely available. That by itself is a serious problem.

There are patient attitudes that affect a lot of cancers. People will watch a cancer grow and not come in because they are afraid of the consequences of a diagnosis.

We were very pleased with the results of the lumpectomy study that was reported last year in breast cancer showing that for early stages a lumpectomy and radiation therapy to the breast was as good as any other operation and the cosmetic effect is near perfect.

That means that a woman who finds a lump in her breast will be more likely to come to a doctor because the procedure required would not be mutilating. There are a lot of women who are afraid to find a lump in their breast because they did not want to lose the breast.

Patient attitudes like that often interfere with using the current techniques. These are serious problems. We have the computer system now that you heard me mention before, called PDQ which has state of the art treatment on it. Every doctor can access the system and find out what it is that can bring the best results.

We are in the process of developing a prevention package for PDQ, called PDQ-P, so that the same information on prevention as well as clinical trials on prevention can be made available.

Mr. NATCHER. What advice do you give to the cancer patient who is seeking the most effective treatment, Doctor?

Dr. DEVITA. Get a second opinion.

Mr. NATCHER. That is good. I agree.

CANCER PREVENTION

What programs does the Institute have in the area of cancer prevention other than discouraging people from smoking cigarettes, Doctor?

Dr. DEVITA. Well, $321 million of our budget is in cancer prevention, research carried on by two of our major divisions. One is the division that concentrates on basic research, the Division of Cancer Etiology, headed by Dr. Richard Adamson, and the second division is the Division of Cancer Prevention and Control, headed by Dr. Peter Greenwald, which takes those findings and applies them in prospective clinical studies to intervene—the 26 studies I referred to.

Most of that is basic research on etiology and other prevention clinical trials. We have about $24 million in smoking prevention trials as well.

Mr. NATCHER. Doctor, is there any reliable evidence that any of these programs are effective in reducing the incidence of cancer?

Dr. DEVITA. We are anxiously waiting for results, of the 26 trials that we have started because I believe if a major study shows that you can intervene prospectively and prevent cancer, it is going to have an enormous impact on people's willingness to do certain kinds of things.

There are some early results that are encouraging. For example, taking vitamin A derivatives as a way of reversing dysplastic changes, not malignant changes, but dysplastic changes in pulmonary tissue, show that these are reversible with certain materials used in clinical trials.

But as of yet, we do not have a prospective study showing the reduction of cancer. We have one study that shows a reduced number of recurrences of polyps in people who have a high propensity for developing polyps, taking micronutrients in a controlled trial at Memorial Sloan-Kettering.

The big study that we started on beta-carotene, the 22,000 physician study is the one that we are anxiously watching.

RESCISSION

Mr. NATCHER. You are requesting a recission of $6,800,000. Now, doctor, assuming the recission is not approved by the Congress, how will these funds be used?

Dr. DEVITA. I think that rescission itself was tied to a reduction of 74 grants that Mr. Early referred to, and my assumption is that will restore those 74 grants.

GRAMM/RUDMAN/HOLLINGS

Mr. **Natcher**. Under sequestration, the budget shows sequestration of $53,868,000 required by the Gramm-Rudman Act in 1986. If you will, give us a breakdown of this reduction and tell us if you plan to seek permission to reprogram any of this money, what about it, Doctor?

Dr. **DeVita**. Undoubtedly we will have reprogramming requests. My own personal preference is to say as long as we hit our targets at the end of the year, please give us some flexibility to move quicker than it takes to get a reprogramming request approved because all the exciting developments I talked about are not in the pockets where we happen to have the money.

That was the genesis of my first comment when I said the number of grants is important. However, both projects like IL-2 and molecular characterization of tumors are not at present done by investigators in the research grant pool. We want to expand those studies, and it may require shifting of money from one pool to another.

AIDS FUNDING

Mr. **Natcher**. Page 19 of your budget, Doctor, shows that you will spend $47,379,000 in 1987 for AIDS research compared to a $26,874,000 in 1985, $27,218,000 in 1986. These figures are correct, are they not?

Dr. **DeVita**. Yes.

Mr. **Natcher**. Do you have assurances that you will receive $47,379,000 for AIDS research from the Assistant Secretary of Health in 1987?

Dr. **DeVita**. We have no reason to expect we will not. These are programs that are high priority. The drug development program that we are running jointly with the National Institute of Allergy and Infectious Diseases is bringing drugs to the clinic this summer. So I am sure we will.

Mr. **Natcher**. Now, Dr. DeVita, I have often said that our Committee needs all the help that it can get. What can our Committee do to help you in the war on cancer? Doctor, from time to time, we listen to you and Dr. Malone, and all of you distinguished men and women that come in here, and then we send the word out generally over the United States to come in and talk to us.

Dr. Malone, we need all the help we can get on this Committee, and I say that to you frankly. What else could we be doing on this Committee, Dr. DeVita, that we are not doing?

Dr. **DeVita**. Mr. Natcher, the Committee has always been extremely generous with the NIH, as you pointed out earlier, and we are very grateful for everything that you have done.

Although some people feel that congressional mandates decrease our flexibility, I am of the opinion that they often reflect the input of your constituents who are our colleagues who are concerned about our own inflexibility in moving into new fields.

The Congress has done a great deal to highlight these areas for us so that we have started some new important initiatives on the basis of congressional input.

That is a good process. I always enjoy coming down and testifying before you.

Mr. NATCHER. We always enjoy having you, Doctor.

Mr. Conte, I yield to you.

Mr. CONTE. Thank you. I will submit some more questions for the record.

SEER PROGRAM

The SEER program, initiated in 1973, also conducts the Institute's surveys on patient survival rates. When will this data collection process really mature? And why is there such a long lag time for receiving the most up-to-date statistics?

Dr. DEVITA. We are always a couple of years behind. Part of the use of the SEER program relates to getting data from the National Center for Health Statistics.

For example, we are dealing at the present time with patients who were diagnosed up to 1981, followed through 1982. So we are four years behind. But more important is that, if you look at five-year survival rates, the 1981 data reflect people who were treated in 1976. So we are, in fact, almost ten years behind in terms of measuring the impact of the most modern treatment. There is probably no way to change that in a system as complex as it is.

But in fact, the system has reached maturity. We have a decade under our belt, and we track our progress, and when we have two decades it will be better. After three, we may not need it any more.

SUPERCOMPUTER

Mr. CONTE. Dr. DeVita, I was amazed last year to find out that the Institute had managed to get funds for a supercomputer without this Committee ever knowing about it. How did you accomplish that feat?

Dr. DEVITA. Well, Mr. Conte, we actually mentioned it to the Committee in the prior year's testimony. We perhaps did not highlight it carefully enough, to bring it to the attention of the Committee because you did mention this point last year as I remember.

What we did, though, is basically shift funds within the same pocket. There was a laboratory chief who left, and we did not reexpand that laboratory but instead used the resources to provide the funds, in part, for the supercomputer.

Mr. CONTE. What are you using it for?

Dr. DEVITA. It can do many things. But one of the things we are doing with it is to keep track of all the sequences that are being put into the Genbank which is the place where the information on the genetic sequences in the genome are kept through program shared by all the institutes.

It can also do very, very exquisite work with the structure of proteins. DNA turns out to be relatively simple but a protein is very complex, and you need to do many, many calculations to determine the structure of a protein, and an oncogene makes a protein. We want to see how it works.

You can twist the protein just a little and then recalculate its structure and how that changes its molecular dynamics. You need very high speed computing power to do this.

You can also determine the structure of whole viruses. Two have already been determined using supercomputers. Perhaps one of the things we can do is to look at the structure of the HTLV-III virus and we may find some hints from the structure as to why it has this genetic drift that allows it to escape antibodies.

There are many powerful things that can be done with it.

Mr. CONTE. Do you have a lot of supercomputers?

Dr. DEVITA. There is only one in the country dedicated to medical research. That is the one at the Frederick Cancer Research Facility.

There are, I think, some 50 other supercomputers in the country in other uses.

CONSTRUCTION

Mr. CONTE. Now, is your line-item for construction the only pot of money available for construction and renovation of extramural facilities? There is no money at all requested this year.

Dr. DEVITA. Currently, in 1987 we have none.

Mr. CONTE. Last year, the Committee provided $3.2 million in construction funds most of which was set aside for one particular center. How many applications for these funds do you get annually, and do you not think the demand will be even higher in FY 87 after the decrease in available funds in FY 86?

Dr. DEVITA. We have been averaging about ten applications per year in the last couple of years.

Mr. CONTE. Just for cancer.

Dr. DEVITA. Yes.

Mr. CONTE. So you are going to be set back a little bit then.

Dr. DEVITA. We will not be able to upgrade, renovate or add on to any of the facilities in 1987.

MONOCLONAL ANTIBODIES

Mr. CONTE. I have been hearing a little bit lately about monoclonal antibodies and the role they can play in diagnosis and treatment of cancer. Can you tell us a little bit about these antibodies and which tumors can be detected and treated by them?

Dr. DEVITA. This is part of the new pathology I was referring to earlier. We can now look at the surface of a cell and make an antibody to specific markers or antigens on the surface of that cell. Their application in diagnosis and classification of tumors is already fairly routine in the lymphoid malignancies—lymphomas and leukemias.

In childhood leukemia it makes a difference in the outcome if you take childhood leukemia that occurs from the B lymphocyte, the B cell goes through a whole series of steps, and they all look the same under the microscope, but when you characterize them with monoclonal antibodies they respond differently to treatment. Knowing that in advance, we can develop different treatments for the ones that do not respond as well.

So monoclonal antibodies in classification and diagnosis have already made an impact. The same thing is now happening in the solid tumors. There is clinical testing in breast cancer and melanoma. There are some responses at Memorial Sloan-Kettering using a monoclonal antibody in metastatic melanoma.

We have high hopes for arming these antibodies as guided missiles, if you will, for specific sites. We have one problem with them. They are made from mouse cells, and when the body sees them, the body recognizes them as foreign elements and sequesters them in the spleen and the reticuloendothelial system.

This year we will be working with what we call hetero antibodies. These are hybrid antibodies that are made with genetic engineering. Half of them, what we call the constant region is from humans, and the variable region, that has to recognize antigens is made from the mouse.

We are hoping that the distribution problem we have at the present time is just a mechanical problem that can be solved in part by doing this. It is a very exciting area.

Mr. CONTE. How much will you spend this year in the research of trying to stop the spread of cancer?

Dr. DEVITA. We have $46 million in monoclonal antibody research.

There is another area, the spread of cancer, metastases, which is a little different, where we have about $17 million, but it is a new emerging area. It is giving us an understanding of how cancer cells get from the primary site to other sites because they do most of their damage when they go to other sites. This is also a very exciting area in research.

Mr. CONTE. Thank you.

Mr. NATCHER. Mr. Early.

CENTERS

Mr. EARLY. Dr. DeVita, the budget indicates that direct costs for competing research centers will be reduced by 20 percent in 1986 and by 25 percent in 1987. And I heard Mr. O'Brien's enthusiasm for centers, and I thought your response was enthusiastic.

Does NCI think we should be reducing the centers?

Dr. DEVITA. We do that rather than eliminate some centers which are an investment. Some of them have been up for ten years. We are spreading the money around to maintain the pool of cancer centers by sharing the resources in that pool.

Mr. EARLY. For the record, what effect these cuts will have on the research programs at the centers, and also for the record, how will the reduction in the size and the scope of the centers programs affect NCI's program plans, both immediate and the long range.

Dr. DEVITA. Certainly.

[The information follows:]

BUDGET LEVEL FOR FY 1987 CENTERS PROGRAM

The budget level for the Centers program in FY 1987 will allow NCI to support the Centers program at the same dollar level as in FY 1986. Those grants that are in a competing status for FY 1987 will be supported at less than the peer-review recommended level. Non-competing awards will also be reduced slightly. In general, we would expect that some of the research conducted under the core grant would be slowed or eliminated and that there would be a reduction of funds available to provide shared equipment and services to investigators located at the Center institutions.

The effect of NCI's program plans are also difficult to project; however, if the Centers must cut back on their research and support efforts, it may make it more difficult to react to emerging priorities.

Mr. EARLY. Doctor, will you be able to start any clinical trials in 1987?

Dr. DEVITA. Yes.

CLINICAL TRIALS

Mr. EARLY. Include that in the record, how many and which ones. Will you have to curtail any ongoing clinical trials with your '87 budget request?

Dr. DEVITA. Yes.

Mr. EARLY. How many?

Dr. DEVITA. I do not know offhand. We have about 600 clinical trials a year rolling over in the groups, and at a slightly reduced level, they will make some choices and curtail some.

[The information follows:]

INITIATION OF MAJOR NEW CLINICAL TRIALS IN 1987

NCI will be inititating seven major new high-priority clinical trials in 1987; the listing follows:

Comparison of Bone Marrow Transplantation with Chemotherapy for Advanced Stage Neuroblastoma.

Clinical Trials using Angiogenesis Inhibitors.

Diagnostic Clinical Trials for Staging and Monitoring Carcinoma of the Prostate and Lung.

Phase III Clinical Trials in Intraoperative Radiotherapy for Intraabdominal Malignancies.

Phase II Studies of Adoptive Immunotherapy of Cancer with Autologous LAK Cells and IL-2.

Treatment/Imaging of Lung Cancer with a Monclonal Antibody Directed Against Bombesin/Gastrin Releasing Hormone.

Adoptive Immunotherapy Utilizing LAK Cells and IL-2 Administered Intraperitoneally for Patients with Ovarian and Colorectal Cancer.

There are a number of other high-priority clinical trials which cannot be initiated because of the funding levels in the FY 1987 request.

Comparison of Post-Operative Radiotherapy and Adjuvant Chemotherapy with Chemotherapy for Treatment of Medulloblastoma.

Treatment of Carcinoma of the Bladder with Hematporphyrin with Photoradiation Therapy.

Use of Tumor Necrosis Factor in Patients with Metastatic Cancer.

Study of Radiolabeled Monoclonal Antibodies to Detect Sites of Hodgkin's Disease Involvement.

Biochemical Modulation of Chemotherapeutic Agents in Colorectal, Breast, Stomach, and Head and Neck Cancers.

Phase II/III Clinical Trials using Hyperthermia in Anatomical Sites.

Phase I/II Trials of Additional Biological Response Modifiers and of Monoclonal Antibodies.

Treatment of Resectable Colorectal Hepatic Metastases with Surgery Followed by LAK Cells/IL-2 Adjuvant Immunotherapy.

Phase III Studies of Adoptive Immunotherapy of Cancer with Autologous LAK Cells and IL-2.

FUNDS REDIRECTION

Mr. EARLY. Include that in the record, please, for the committee. Doctor, with regard to molecular characterization of cancer therapy in children, is your budget set up in such a way that you must redirect only treatment dollars and staff as a means of spending more on this exciting and unanticipated breakthrough or will you be able to take money from other pools within the budget, for instance, the research project pool which I believe is the largest part of the NCI budget and the pool that has received the most increases in recent years?

Dr. **DeVita**. The way the budget is being handled now, Mr. Early, is that all the institute budgets are being pooled together apportioned, if you will, as one budget at the NIH level, and then it is apportioned with about 20 different budget line controls so that in order to go from one pocket to another, we need to go to NIH to get approval, within their level of flexibility, and from there to OMB if NIH does not have the flexibility.

My point earlier about having fewer steps was related to the apportionment process. Basically in all fairness to OMB, I do not really mind dealing with OMB rather than NIH, just not both. I do not like dealing with more organizations than you have to deal with to make a small decision relative to a billion dollar budget.

Mr. **Early**. They are not going to make the final decision.

Dr. **DeVita**. They are probably no less likely or no more likely to say no than other administrative units such as NIH we have to go to for decisions for day-to-day operations.

Mr. **Early**. I think almost everyone agrees you should have the flexibility for that, and that is as big a threat as these cuts to me. I think the flexibility is really diminishing.

Mr. Chairman, I have several other questions but because of time, I will put them all in the record if that is all right.

Mr. **Natcher**. That will be fine.

Mr. O'Brien.

Mr. **O'Brien**. Thank you, Mr. Chairman. I will have a few questions for the record.

Mr. **Natcher**. Dr. DeVita, we want to thank you and your associates for appearing before our Committee at this time on behalf of your budget request for the fiscal year 1987.

It has been a good hearing, Doctor. We appreciate it.

The Committee will now recess until 2:00 this afternoon.

[The following questions were submitted to be answered for the record:]

ACQUIRED IMMUNE DEFICIENCY SYNDROME

Mr. Conte. From reading your justifications, and looking at a lot of the information we have about AIDS, it seems that the AIDS virus has affected a lot more people than just those with visible signs of the disease. Do you have any figures on the proportion of actual AIDS cases compared to those with only a positive sign of the virus?

Dr. DeVita. The most definitive study to date was published in Science in February of 1986. The senior author of this article is Dr. William Blattner, a staff epidemiologist of the NCI. Dr. Blattner and his associates studied more than 700 people for signs of HTLV-III infection and signs of the development of AIDS. Those studied were persons of high-risk groups; that is homosexual men, parenteral drug users, and hemophiliacs. There researchers found that in individuals who began to show a positive sign of the virus (became antibody positive) 10.1 percent of those individuals developed AIDS over a three year observation period. Most experts estimate that more than 1,000,000 Americans may be infected with the virus at this time. These data suggest that more than 100,000 individuals are at risk for developing AIDS within the next three years.

Mr. Conte. I know this issue has created a lot of waves down at the Defense Department, Doctor, but I'm going to ask it anyway. Do you think we know enough about this disease to take clear steps, and make concrete recommendations to that large group of people who only show traces of the virus?

Dr. DeVita. First, let me briefly review what we know about the disease. We have evidence that, of people who are infected with the virus, approximately three percent per year will develop AIDS. Many more, possibly in excess of 10 percent per year, will develop a lesser form of the disease called AIDS-related complex or ARC. We know that both AIDS and AIDS-related complex are deadly manifestations of the infection. We know that the virus can be transmitted by blood products, by male-to-male sexual contact, and male-to-female sexual contact. Recent evidence suggests that female-to-male sexual contact may also spread the infection. I therefore think that concrete recommendations can be made with respect to taking steps to curb the transmission of the disease. Studies are now in progress to determine what recommendations can be made with respect to the administration of specific anti-AIDS therapy.

Mr. Conte. What is the total funding available for AIDS research in the Institute in FY 1986, and does all of that come from the amount we specifically gave you, or is some of it derived from other sources?

Dr. DeVita. In FY 1986, the NCI has $27.2 million budgeted from its appropriated funds for AIDS research efforts. In addition, NCI will administer the obligation of $13.5 million appropriated to the NIH Office of the Director for clinical initiatives in AIDS research.

Mr. Conte. Yesterday, Dr. Wyngaarden told us that about the only area where OMB gave you what you requested was in the area of

AIDS research. How much is the Institute proposing to spend on AIDS in FY 1987, and in your professional judgment will that amount meet the need?

Dr. DeVita. Currently, the NCI anticipates expenditures of approximately $47.2 million for AIDS research in FY 1987, which includes continuation costs of the clinical initiative funded out of the Office of the Director, NIH, which NCI will administer in FY 1986. This anticipated budget has been transferred to the Office of the Assistant Secretary for Health to consolidate AIDS efforts. Based on our current knowledge, these amounts will be sufficient to support planned activities in AIDS research.

LUNG CANCER

Mr. Conte. Lung cancer is probably the deadliest form of cancer we know. What kinds of programs is the Institute conducting to target women and minorities to help bring their rates of lung cancer down?

Dr. DeVita. Although lung cancer rates among some portion of white males may be declining, this is not the case for other portions of the U.S. population. Among black and Hispanic Americans and all women, smoking-related cancer rates continue to rise. The following programs are supported:

> Black Americans: Three intervention studies have been funded through the Smoking, Tobacco and Cancer Program (STCP) which will reach over 55,000 black smokers. Intervention strategies to be tested include the use and potential role of black physicians in delivering smoking cessation strategies to black patients, self-help smoking cessation approaches, and community-based smoking prevention and cessation campaigns. Additionally, the Office of Cancer Communications has mounted an information campaign, a major portion of which is devoted to smoking, which is aimed specifically at black Americans. As part of its minority field program, the Division of Cancer Prevention and Control has also issued three additional Requests for Proposals (RFP) for intervention research projects in the black population. They are entitled "Primary Prevention of Cancer in Black Populations", "Avoidable Mortality of Cancer in Blacks", and "Quality Control Research in Blacks". We expect these intervention studies to reach over 55,000 black smokers.
>
> Hispanic Americans: The STCP currently supports four interventions trials that are aimed at Hispanics. Under current evaluation are smoking demography and correlated health behaviors among Hispanics as well as smoking control interventions. These interventions include mass-media campaigns, school-based prevention strategies, group "cohesive" sessions, community organization and training, and systems of social support for coping with stress. In recognition of the diversity of the Hispanic population of the U.S., these trials are being conducted in the Northeast, Southwest and far-West. Additionally, both Hispanic adolescents and adults are being targeted, with nearly 1,000,000 Hispanic smokers being at least indirectly impacted by this research.

Women: The STCP intervention research that is targeted to women focuses on social, cultural, psychological and economic factors that influence female smoking, influencing factors such as the media, the changing roles of women, fears of weight gain, and stress management. Four intervention research trials that are aimed exclusively at women who smoke will begin in FY 1986.

These trials will impact on approximately 40,000 women smokers. The number of women reached through the STCP and the portion of the budget aimed at women, however, is substantially greater than this because women are included in each of the 35 intervention trials being supported by the STCP, although only four of these trials are focused exclusively on women.

In summary, the NCI is quite concerned about the rising incidence of lung and other smoking-related cancers among women and black and Hispanic Americans. Intervention research with a public health goal has been initiated with each of these populations at risk.

TRANSFER OF RESEARCH ADVANCES TO PATIENT CARE

Mr. Conte. One thing we've discussed often in the past is the general ability to move from advances in the laboratory to actual changes in the way doctors treat their patients. The pace of change is so rapid these days it would seem that we're always behind. What can you say about the Institute's ability to get the word out after a useful discovery is made? Will you be able to keep up an effective, efficient process with this budget request before the subcommittee?

Dr. DeVita. Over the past several years the Institute has developed a strong capacity to keep both the public and health professionals informed about important new research findings.

For example, the NCI Office of Cancer Communications, which deals primarily with the public, has highly developed channels to reach not only the general public, but patients as well. Important research findings are communicated to the press, so that the findings are widely disseminated to the public. In addition, each year NCI distributes about 20 million publications that summarize and highlight research findings from many studies. They are designed to provide people who are at risk of cancer with information that can help reduce risk, and to provide cancer patients on how to deal best with their disease, and live most comfortable with their treatments. The Institute also supports a toll-free telephone service that now receives 400,000 calls annually. The latest information is available to those who call the toll-free number; in fact, NCI communicates with those who answer the telephone via electronic mail so that the latest information is always in the hands of those answering inquiries. The toll-free phone service is heavily promoted by NCI and various cancer centers.

For health professional, there are a number of traditional communications techniques used. In recent years, NCI has pioneered the use of innovative techniques to keep health professionals informed of the latest developments. One way has been to involve community physicians, for example, in the research itself. Treatments available in research protocols are considered to be on the leading edge of cancer medicine, so physicians who participate in research have a better chance of staying current with the rapidly improving treatment techniques. Another way was the development of a computerized database - a living textbook of the most current cancer treatment information - that is available to any doctor who has access to a personal computer with a telephone hookup, or to a medical library. The information in the database itself is updated by an editorial board monthly. Advances that occur in between the monthly updates are flagged for doctors who use the database. This is done through a special "news" bulletin that can be inserted into the database in minutes.

With the budget request before the committee, NCI will be able to maintain these activities, which have a high priority within the range of NCI program activities.

Mr. Conte. Do you have any rough projections on the average length of time it takes to move from advancements in the lab to actual improvements in patient care?

Dr. DeVita. Certainly one of the important goals of the National Cancer Program is to expedite the implementation of advances in our understanding of basic cancer biology with the goal of improving treatment of cancer patients. As a point of reference, during the 1970s, it took an average of seven years for a new drug with anticancer activity to make the transit from initial discovery to first use in patients in clinical trials. An additional seven years was required to complete all phases of experimental clinical testing necessary before the drug could be proven effective and marketed.

Clearly, a 14 year timetable for implementation is unacceptable in our current scientific climate where basic research observations with important treatment potential are made with ever increasing frequency. The National Cancer Institute has responded to the challenge of expediting clinical trials with promising agents in a number of ways including: 1) establishing improved working relationships with private sector industry and the Food and Drug Administration (FDA); 2) streamlining the preclinical investigations required before an agent can be used in patient treatment; and 3) maintaining an activist approach to assure that the most promising cancer treatments reach patients quickly. The result is that new effective treatments are often being given to patients in clinical trials within one or two years of discovery.

For example, Dr. Samuel Broder at the National Cancer Institute (NCI) discovered that the drug azidothymidine was effective in inhibiting the growth of the AIDS virus in test tubes. By working closely with FDA and a private sector pharmaceutical firm, Dr. Broder was able to treat his first patient within five months of his initial laboratory observation. The results of this clinical trial, recently published in the medical journal, Lancet, indicate that azidothymidine suppresses virus multiplication in patients and may reverse some features of immune deficiency.

A second example of rapid implementation of a new discovery is the LAK/IL-2 treatment. In 1980, Dr. Steven Rosenberg discovered that Interleukin-2 (an immune system activator) could convert white blood cells into lymphokine-activated "killer cells". In 1984, genetic engineering techniques allowed large amounts of this substance to be synthesized for the purpose of treating patients.

In December 1985, Dr. Rosenberg reported that adoptive immunotherapy using Interleukin and activated killer cells successfully activated the immune system to destroy cancer cells in 11 of 25 patients with advanced cancers. Importantly, this new treatment was effective in cancers such as kidney cancer, colon cancer, and melanoma skin cancer, where little effective treatment exists today. In February 1986, the NCI selected six medical centers nationwide to offer this new treatment with NCI support.

Preclinical drug development procedures are being streamlined in other areas as well, including biological response modifiers and standard chemotherapy. For example, the NCI and FDA have agreed upon streamlined preclinical toxicology studies which save time, expense, and animal resources without compromising patient safety. In addition, in order to expedite clinical trials still further, the FDA now review NCI requests to use promising new anticancer agents within 60 days of receipt. Animal pharmacology studies are planned to guide dosing in patient clinical trials, a step which in itself will decrease the time to complete these studies by 50 percent.

In summary, laboratory observations with important treatment promise are now reaching patients within a few years of this discovery. The expedited clinical use of new treatments is an important priority of the National Cancer Program and has been achieved both by the compelling promise of basic research advances and increased cooperation between NCI scientists, the FDA, and the private sector.

Mr. Conte. In your justifications, under the Surveillance, Epidemiology, and End Results (SEER) program you mention an initiative, coordinated with the Centers for Disease Control, to assist state and local agencies in addressing the specific cancer problems facing their region. Can you tell us a little about this?

Dr. DeVita. The purpose of the NCI's public health agency initiative is to increase the quantity and quality of cancer prevention and control programs conducted by state and local public health agencies and to promote the development of programs that are consistent with NCI's year 2000 goals and objectives. Begun a little over two years ago, this initiative's activities include: 1) direct technical assistance; 2) promoting information exchange; and 3) encouraging the development of technical capabilities in cancer prevention and control at the state and local levels. The primary means of implementing this initiative include: 1) direct staff interaction with agency personnel at the state and local level through on-site visits or through phone/mail interactions; 2) developing and disseminating information on cancer control science and activities undertaken by others; 3) funding of demonstration projects to evaluate methods of implementing cancer prevention and control intervention programs in public health agency settings; and 4) coordinating activities to take advantage of existing knowledge and to avoid duplication of effort with other Federal agencies that interact with state and local public health departments. This program is being developed with the advice of a working group that includes a number of state, city and county health officers and cancer prevention and control program staff at the state level, as well as staff from the Centers for Disease Control.

Mr. Conte. Have many states and localities expressed an interest in this type of program?

Dr. DeVita. The initial response to the public health agency initiative has been much greater than anticipated. Numerous interactions with state and local departments have occurred over the short history of this program. These have covered a wide variety of technical content and have ranged from superficial to intensive levels of discussion. A current measure of the amount of interest in this program is provided by the recent response to our Request for Applications from public health agencies for demonstration projects in developing technical capabilities leading to cancer prevention and control intervention programs at the state and local level. Twenty-nine applications were received, 25 from state health departments and the remainder from city and county health departments.

Mr. Conte. Can you provide us a list of the agencies with which you have begun discussions?

Dr. DeVita. Yes. The following is a listing of the applicants to the Request for Applications noted above:

Allegheny County (Pennsylvania) Health Department
Arkansas Department of Health
Baltimore City (Maryland) Health Department
California Department of Health Services
Colorado Department of Health
Connecticut State Department of Health Services
Florida Department of Health
Georgia Department of Human Resources
Illinois Department of Public Health
Iowa State Department of Health
Los Angeles County (California) Department of Health Services
Maine Department of Human Services
Maryland State Department of Health and Mental Hygiene
Massachusetts Department of Health
Michigan Department of Public Health
Minnesota Department of Health
Missouri Department of Health
Monroe County (New York) Health Department
Nebraska Department of Health
New Hampshire Department of Health and Human Services
New Jersey Department of Health
New York State Department of Health
North Carolina Department of Human Resources
Ohio Department of Health
Oklahoma Department of Health
Rhode Island Department of Health
South Carolina Department of Health
Utah Department of Health
Washington State Department of Health

Mr. Conte. Are you requesting an appropriation to begin funding proposals in FY 1987?

Dr. DeVita. Funding for the technical development will be initiated in FY 1986 and the President's Budget request includes continuation funds for ongoing grants as well as funding for a second Request for Applications for additional demonstration projects in health departments. We anticipate that four to six of the above agencies will be funded.

CANCER IN HISPANICS

Mr. Roybal. The Secretary's Task Force on Black and Minority Health indicated that there is a significant lack of data on the health status of Hispanics, including cancer rates. What special effort, if any, is being taken by the National Cancer Institute to address the data issued regarding cancer in Hispanics?

Dr. DeVita. The NCI has developed a Hispanic Cancer Control Program (HCCP) to address a number of issues regarding cancer in Hispanics. Because of the dearth of data on cancer in Hispanics two priority areas for the HCCP are data collection and data analyses. Current plans for data collection include over-sampling Hispanics in the Cancer Control Supplement to the 1987 National Health Interview Survey (NHIS) which is conducted by the National Center for Health Statistics and the Bureau of the Census. With the NCI Surveillance, Epidemiology and End Results (SEER) program recently adding the state of New Jersey to its data collection efforts, more data may be collected on cancer incidence and survival rates for Hispanics in New Jersey. Data analyses are being planned for information from the NHIS supplement as well as from the the Hispanic Health and Nutrition Examination Survey. Also, a study has been commissioned by the HCCP which is examining data sources for information on cancer in Hispanics related to the Institute's cancer mortality reduction objectives. This study will identify data sources which contain information on Hispanics, both published as well as not published, and identify gaps of information about cancer in Hispanics insofar as such information would relate to monitoring progress toward achieving the mortality reduction objectives for Hispanics.

Mr. Roybal. Recent studies indicate that low socio-economic status (SES) may be a primary risk factor regarding excess rates of cancer in these groups. Hispanics as a group have about 30 percent of the population below the poverty line as well as high drop-out rates from school and high unemployment rates. Has there been any specific data on Hispanics as a low SES group in relation to the incidence of cancer in the population?

Dr. DeVita. To date there are no specific data on Hispanics as a low SES group in relation to the incidence of cancer in the population. A review of the literature on the issue of low SES as a risk factor was commissioned by the American Cancer Society, but this review dealt mainly with the black population. Through our SEER program, data is collected on a sample of the U.S. population, that does provide data on the incidence of cancer in various regions of the nation. This then permits analysis of cancer and its association with specific segments of the population.

Mr. Roybal. Since the Hispanic population is such a young group (average age is about 23), and since most types of cancer occur later on in life, what measures are being taken by NCI or have been planned to prevent cancer in this young population?

Dr. DeVita. Current efforts being taken by NCI in preventing cancer in the Hispanic population include the funding of four research projects related to smoking and Hispanics, and one research project regarding health education for cancer screening and detection for elderly Hispanic women. Of the former projects, two attempt to prevent smoking in high school age youth and in junior high school students, while another project attempts to provide intervention for Hispanic young adults to stop smoking. The fourth project on smoking will demonstrate and analyze the effects of mass media and community organization and training to reduce cigarette smoking in specific low income populations near the Mexican border.

Besides these projects, the Hispanic Cancer Control Program (HCCP) is now planning specific courses of action NCI might take in the prevention of cancer in the Hispanic population. In April 1986 the HCCP is convening a workshop for identifying NCI Hispanic program priorities and directions. Participants will be experts on concerns of the Hispanic population and/or on Hispanic cancer issues. Results of this workshop will provide recommendations for actions to be taken by the NCI HCCP.

PREVENTION ACTIVITIES

Mr. Roybal. The NCI goal of a 50 percent reduction in the cancer mortality rate by the year 2000 would seem to depend heavily on preventive measures. What are the total NCI dollars obligated for prevention activities working toward this goal?

Dr. DeVita. In total, the Institute projects it will obligate $344.9 million on prevention activities in FY 1987.

Mr. Roybal. How much of this is being used for Hispanics?

Dr. DeVita. NCI dollars budgeted for activities targeted to the Hispanic population in FY 1987 are $2.1 million, of which $1.9 million is for smoking-related projects and $150,000 is for cancer communications among Hispanics. It is highly likely that prevention research in general and not specifically targeted for this population will also benefit Hispanics.

Mr. Roybal. Prevention should be a major effort at NCI. Yet, the NCI Cancer Prevention and Control line is about $64.0 million of a $1.1 billion budget. Why is it such a small part of the NCI budget?

Dr. DeVita. Actually, prevention activities are not funded solely out of the Cancer Prevention and Control line. The 26 prevention clinical trials that you have undoubtedly heard about are funded here, however, most other prevention activities are funded under the Cause and Prevention research thrust. Cancer Prevention and Control provides the impetus and is the foci for all NCI prevention work, which approximates $344.9 million, or about one-third of the NCI budget.

REPROGRAMMING

Mr. Roybal. Have you received any special instructions from OMB on how to manage the NCI reprogramming activities. If so, what are those instructions?

Dr. DeVita. The instructions that we have received regarding the redistribution of funds require that any adjustment, either increase or decrease, should be requested of the NIH Director. This is controlled by each mechanism line, for each appropriation. However, for research project grants, further control is a limitation that precludes the movement of the number of awards and/or any funds amongst non-competing (T-5), new (T-1) and competing (T-2), supplemental (T-3), within research project grants. This same restriction is also applicable to the cancer centers line where the control is between new/competing renewal grants and non-competing/supplements.

SMOKING CESSATION

Mr. Roybal. What level of NCI funding was devoted to smoking cessation research activities in FY 1985 and is anticipated in FY 1986 (post-sequestration) and in FY 1987? What percentage of those funds were specially targeted toward adolescents, women and minorities?

Dr. DeVita. In FY 1985 $21.1 million was obligated on smoking and cancer research. In FY 1986 and FY 1987, projections call for $23.3 million and $24.7 million, respectively, to be spent on smoking and cancer research. Of these amounts, 59 percent was obligated in FY 1985 on efforts aimed towards adolescents, women and minorities. In FY 1986 and FY 1987, respectively, this effort will increase to 66 percent and 74 percent.

REDUCTIONS IN 1987 BUDGET

Mr. Roybal. The 1987 budget shows substantial reductions in contracts and "other services" from the 1985 level. How much, if any, of the scientific work that was being done under the contract mechanism is being terminated prematurely or modified in ways that will impact significantly on the scope of activities or the timeframe for completing the work? Would any area of extramural or intramural research be affected disproportionately by these reductions and, if so, were those reductions based on program priority or on categorical expenditure targets imposed upon NCI?

Dr. DeVita. Reductions in contracts and other services from 1985 to 1987 have occurred in response to efforts to increase funding of research grants by approximately $15 million while the total NCI budget has been reduced by five million dollars. While the mechanism of funding has shifted from contracts to grants, and the individual investigators and institutions receiving support have changed, the overall scientific programs have not been severely impeded. NCI will attempt to fund the highest priority research regardless of its mechanism of support.

The reduction in other services reflects the effect of some of the economies NCI plans to implement in response to the Gramm-Rudman-Hollings legislation.

INITIATIVES ON CANCER RATES IN MINORITY POPULATIONS

Mr. Roybal. What impact, in terms of number of dollars or specific numbers of projects, would the 1987 budgetary reduction have on recent NCI initiatives targeting the higher rates of cancer in minority populations?

Dr. DeVita. Until we know the number of and relative merit of proposals in response to recent NCI initiatives targeting the higher cancer rates in minority populations, it will be difficult to itemize the impact of the 1987 budget for these initiatives. There are several options available for NCI in this regard and in consultation with our Advisory Boards we could consider: 1) reducing the number of awards for existing initiatives; 2) reducing the level of effort for any one award; or 3) delaying the onset of proposal initiatives.

TRANSFER OF RESEARCH TO COMMUNITY PRACTICE

Mr. Roybal. NCI estimates that 40,000 people could be saved by receiving state-of-the-art treatment. What problems are preventing these people from receiving the best available treatment? What proposals, in addition to the PDQ and CCOP, have been made within the Institute for moving the state of the art out into the community more rapidly or more comprehensively? Are any of these activities being delayed because of budgetary constraints?

Dr. DeVita. The issue of the availability and use of state-of-the-art treatment is an extremely complex problem involving barriers at the personal, social and provider levels. In addition to PDQ and CCOP, the Institute is involved in the following:

- The Cancer Information Service (CIS) continues to directly provide information on sources of cancer treatment through its 20 regional offices, which cover 75 percent of the population, and through its national office, which serves the remainder of the population. Each of these offices is computer-linked to PDQ. In 1985, 15.6 percent of all inquiries to the CIS were related to cancer treatment, and over 16,900 inquiries were related to clinical trials alone. The CIS referred more than 27,600 people to NCI-sponsored clinical research programs in 1985.

- To identify and correct social barriers to state-of-the-art cancer care, the Institute is supporting research studies such as the "Black/White Survival Study", to identify reasons for the significant differences in survival between these two population groups, and the "Avoidable Mortality from Cancers" initiative, which concentrates on identifying factors that contribute to cancer deaths that should have been avoided (e.g., cervical cancer deaths) and then tests community interventions to reduce or eliminate those factors.

- To address dissemination of information to providers of state-of-the-art treatment, the Institute is sponsoring an evaluation project to determine the effectiveness of existing hospital tumor boards on cancer care. Staff of the Centers and Community Oncology Program are developing detailed cancer site plans covering the latest information on cancer prevention, early detection and state-of-the-art treatment. Upon completion of these (later this year), NCI staff will hold meetings with the leaders of the provider professional societies to plan for their direct involvement in moving state-of-the-art information out to their members in a timely and efficient manner.

At this time, none of the these initiatives are affected by budget constraints except for the Cancer Information Service, where it was not possible to fund all of the technically acceptable proposals for regional offices during its recompetition in 1985. Selected reductions in individual regional office budgets may be necessary in FY 1987.

AIDS RESEARCH

Mr. Roybal. What assurances can you provide that the rescission proposal on the creation of a reserve of animals for the testing of an AIDS vaccine does not pose any risk of delaying human vaccine development?

Dr. DeVita. Testing of AIDS vaccine preparations in the NCI's vaccine development area follows an orderly progression from lower species to higher primates. The quality of a response to an antigen first has to be ascertained in species which are readily available before testing a vaccine in the rare chimpanzee, which is an adequate model for the testing of whether a vaccine could prevent infection by challenge virus. NCI has already committed some funds for accessing an initially adequate number of chimpanzees, assuming there are no serious scientific obstacles. However, long-term commitment for the holding of vaccinated animals will probably be required. If unforeseen difficulties arise, then more chimpanzees may be needed, and development of a replacement base will be needed as well. In summary, development of an AIDS vaccine for use in man is not being delayed, based on currently available data.

Mr. Roybal. With the proposed change to consolidate the funding in the Office of the Assistant Secretary for Health, do you have assurances that the current NCI commitments for AIDS research will be honored? What role will NCI play in the process of determining how AIDS funds would be distributed among the various Public Health Service agencies?

Dr. Devita. Yes, we have that assurance. Although NCI does not directly partake in the determination of the distribution process, NCI has a voice in the NIH AIDS Committee, and Drs. Wyngaarden and Fauci transmit NCI's needs to the decision point operation in OASH.

MORTALITY RATES AMONG MINORITIES

Mr. Stokes. Former Secretary Margaret Heckler's Task Force on Black and Minority Health found that cancer is a major cause of excess deaths among minorities. Blacks have the highest overall cancer rates for both incidence and mortality of any population group in the United States. The Task Force identified a number of areas where additional research, outreach and education is needed. Dr. DeVita, what will you do differently this year in order to respond to the recommendations of the Task Force report?

Dr. DeVita. The findings and recommendations of the Task Force concerning cancer were provided largely by NCI, and reflect a vastly increased interest in this problem within NCI. An appendix volume to the Task Force report characterizing the cancer needs of minorities has been prepared by NCI and delivered to the Secretary's Task Force. Additionally, the most detailed statistical compendium ever on cancer in minorities is being published by NCI on March 31, 1986. This compendium contains all available data that describe this serious problem. It was prepared so that researchers can formulate hypotheses for causes and discrepancies in cancer rates and propose interventions to reduce those rates; so that planners can identify new program options for improved health protection; and so that policy makers can determine necessary resource allocations. In short, by codifying these statistics, NCI is making a major scientific contribution that will enable our society to address the problem and correct it.

Our year 2000 goal, which aims to reduce cancer mortality rates in the nation by 50 percent, has an additional goal as well: to eradicate differentials in cancer rates between racial-ethnic groups.

To meet this goal, NCI has been working hard to upgrade its intervention research program in this area. For the past year and a half, we have been working closely with the leadership of the representative medical and public health communities. Because the cancer problem among blacks is quite serious, and because much of the available data is on this population segment, we have focused our initial emphasis there. Consequently, priorities have been established in the following areas:

- Reducing cancer risk factors, such as smoking.
- Increasing cancer-related knowledge, attitudes and practices.
- Better use of health resources, including access to, availability and utilization of screening and detection services.
- Reducing the stage of disease at diagnosis.
- Enhancing the quality and continuity of, and compliance with, treatment.
- Reducing delay in seeking treatment following symptom onset.

Our general approach in implementing this program has and will continue to include the following elements:

- Working with the representative medical and public health communities to assure sensitivity to the complexity of the problem and responsiveness to the needs of researchers committed to this area.

- Defining the problem to the extent that the state-of-science permits, and focus attention on promoting research leading to effective interventions where cancer rates can be reduced the most.

- Promoting intense interaction between NCI and the research community to assist, support and stimulate researchers to take on this very difficult and challenging problem.

Some early results from these efforts are encouraging and indicate some early successes:

- A major study on survival differences between blacks and whites that was started in 1984 now provides leads where new research can be focused.

- In 1985, the first studies on smoking interventions specific to blacks and Hispanics were initiated.

- A growing number of minority investigators are applying for cancer control funds. This is especially promising because the aim of this program is to bring new investigators into the field.

- The response to three RFPs on cancer prevention and control interventions in black populations stimulated a much larger number (41) of proposals than expected; up to 11 awards will be made this summer.

- A planning grant application for a Consortium Cancer Center submitted by three predominantly minority medical schools received an excellent priority score and an award will be made very soon. This consortium is significant in that it focuses on cancer prevention and control research in blacks in response to our year 2000 goal.

NCI's Office of Cancer Communications is making major efforts to get cancer information to minorities:

- Pilot information projects are beginning in five areas of the country: Detroit, Michigan; Atlanta, Georgia; Grambling, Louisiana; Chicago, Illinois; and the state of North Carolina.

- The National Cancer Institute is providing technical assistance and consultation on cancer education to the National Council of Negro Women, the American Cancer Society, the Department of Health, and the Council of Churches, for a project in Washington, D.C.

These community-based projects are being designed around the needs of each area and in concert with available resources at the Federal, state and local levels.

- In Detroit, the National Association for the Advancement of Colored People is serving in a general leadership role, with direction from the medical community.

- In Atlanta, Emory University, Morehouse School of Medicine, Clark College, other black colleges and universities, the National Black Nurses Association, the National Medical Association, and other groups are mobilizing to address the health needs of the black community.

- The Shriners are working with the staff of the Governor's office to promote a cancer prevention awareness program in the State of North Carolina.

- Grambling University is serving as the focal point for an information and education program in their northern parish of Louisiana.

- In Chicago, the Portes Center (a diagnostic and educational facility) has expressed an interest in developing an awareness program targeting minority populations. This project is in its formative stages.

The National Football League (NFL) is assisting the National Cancer Institute in its education efforts by assigning football players to help in each NFL city, and through other mass media projects. For example, the American Association for Retired Persons has produced a television public service announcement featuring Rosie Greer, a retired NFL player. NCI served as liaison and provided consultation to the project.

While these projects are being implemented, the National Cancer Institute is engaged in planning projects in other areas of the country and with other organizations representing black interests and concerns. For example, the Medical Director of the Shriners is being identified as the liaison for a project in New York City. In Los Angeles linkages are being made between black churches, the Cancer Information Service, and groups involved in health advocacy. Plans are being formulated for extended initiatives with black churches and colleges. In addition, a working group meeting is being planned for fall 1986 to develop the capabilities of the Cancer Information Service for outreach to minority populations.

A closely related intra-Institute initiative involving the Office of Cancer Communications and the Division of Extramural Activities will research ways to effectively disseminate health information to the minority community utilizing two-year and four-year minority colleges.

Another program, the Minority Satellite initiative, contributes to the support of NCI and Clinical Cooperative research groups to better enable the NCI research to reach and support minority populations which are particularly susceptible to cancer. Since blacks have a significantly higher cancer mortality rate than the American population at large, this initiative is important to the goal of reducing cancer mortality. The program is expected to improve cancer education in the underserved population as well as increase physician participation and patient enrollment into well-designed and well-implemented clinical trials.

NCI is continuing efforts to increase the number of minority investigators involved in all areas of cancer research through our Minority Investigator Supplement and our co-funding efforts with the Division of Research Resources.

Additionally, NCI is planning the following activities for this year:

- In the Division of Cancer Prevention and Control, a Branch to address the needs of special populations is being created. It will focus on research directed at the cancer problem in minorities and the group at high risk for premature cancer mortality.

- The current initiative on cancer prevention and control intervention research in blacks will be expanded if resources become available. In particular, development of the Network of Cancer Control Research in Black Populations will continue to be a major area of emphasis.

- Program planning for Hispanic populations has been proceeding and the first intervention research initiatives will begin later this year.

- The needs of other minorities will be addressed as resources permit.

MAJOR CANCER INITIATIVES FOR MINORITIES

Mr. Stokes. Page 46 of the budget justification refers to "a special initiative to address cancer problems in minorities, with early emphasis on black Americans". Please elaborate on the four major initiatives identified in the justification and indicate the funding allocated for each initiative in 1985, 1986 and 1987.

Dr. DeVita. The major initiatives you refer to are:

1) The Cancer Prevention Awareness Program for Black Americans, initiated in May 1985, is designed to tell individuals how they can reduce their risk of cancer. It features mass media messages to help create more awareness in the black community, and community education programs that are assisted by black church groups, educational institutions, health and medical societies, sororities and fraternities, and other community organizations. In addition, the National Football League (NFL), which has many black players, has joined NCI and will support dissemination of cancer prevention messages in each NFL city, using black football players as exemplars. The funding for this initiative in 1985 was $300,000; in 1986, $350,000; and in 1987, $400,000.

2) Development of the Black Research Network will foster research capabilities and form a critical mass of investigators interested in conducting research to decrease

the burden of cancer in blacks. Two developmental meetings organized by NCI were held recently. The first was at the Morehouse School of Medicine, Atlanta, in December. The second, held in February, was at Meharry Medical College in Nashville. This year meetings will be held in Los Angeles at the Charles Drew Postgraduate School of Medicine, and in Washington, D.C. at Howard University. The network has significant long-tern potential, because it aims to set research priorities, foster the exchange of information, and enhance the capabilities of researchers devoted to these important problems. The funding for this initiative in 1985 was $40,000; in 1986, $70,000; and in 1987, $100,000.

3) Additional solicitations are as follows: (a) Research contracts on primary prevention in blacks will focus on intervention research in smoking prevention and cessation. Proposals have been received and up to five awards are anticipated for FY 1986; (b) Research contracts on avoidable mortality from cancers in blacks will focus on intervention research to reduce or eliminate risk factors that lead to avoidable deaths from cancer. Proposals have been received and up to five awards are anticipated in FY 1986; (c) A research contract on analytic support and quality control will focus on providing technical support and research coordination to investigators engaged in the two other groups of contracts. The funding for this initiative was zero in 1985; $1,474,000 in 1986; and $1,995,000 in 1987.

4) The Comprehensive Minority Biomedical Program (CMBP) includes several initiatives. These include an intra-Institute effort to find ways to disseminate effectively health information to minorities by using the resources of traditionally minority colleges. Another initiative supports treatment research groups to help assure that research reaches and supports minority populations which are susceptible to cancer. This program not only is expected to improve patient education, but will also increase the participation of minority physicians and patients in well-designed and implemented clinical trials. This Program also works to increase the number of minority investigators participating in cancer research. The funding for this initiative was $3.3 million in 1985; $3.3 million in 1986; and $3.4 million 1987.

MINORITY FIELD PROGRAM

Mr. Stokes. What is being accomplished through the Minority Field Program?

Dr. DeVita. The Minority Field Program is one of several NCI programs that address the issue of minorities and their cancer rates. Its specific mission is to foster the development of intervention research designed to reduce the burden of cancer in minority populations. This program has been in development for approximately 20 months. Because blacks experience some of the worst differences in cancer incidence, survival and mortality rates when compared to the U.S. population as a whole, emphasis has initially been placed on developing programs for this population. To date, the following has been accomplished:

- A number of formal planning activities involving leaders of the black medical, research and public health communities have been completed. Specifically, five major planning meetings have been convened by NCI and several other smaller planning sessions have been held at minority institutions or in conjunction with professional scientific meetings.

- Available statistical data have been collected and analyzed to characterize the problem of cancer in black populations. A major report, "Cancer in Blacks and other Racial-Ethnic Groups: Statistical Profiles", is being published by NCI in the spring of 1986, for use by concerned scientists, planners and policy makers. This is the most complete statistical compendium on the subject to date.

- A review of all research studies that may have implications for cancer prevention and control related to black populations is underway. An annotated bibliography will be published later this year.

- Staff support for the Secretary's Task Force on Black and Minority Health was provided for the cancer content in the report. A separate report further detailing the cancer problem has been prepared for publication as an appendix to the Task Force report.

- Three Request for Proposals for intervention research in black community settings have been issued and proposals received: 1) Primary Prevention of Cancer in Blacks; 2) Avoidable Mortality in Blacks; and 3) Analytical Support and Quality Control Unit (for the first two studies).

- NCI has provided staff and fiscal support to the development of the "Network for Cancer Control Research in Black Populations". Two meetings of the Network have been held and two others are planned for this year.

- In addition, staff have continued to respond to a heavy volume of requests for technical assistance and scientific advice, made multiple presentations to professional audiences on the cancer problem in black populations and NCI initiatives, and prepared five articles for publications in scientific journals.

Mr. Stokes. What resources have been allocated to this program in 1985, 1986 and 1987?

Dr. DeVita. The NCI has allocated the following levels of support to the Cancer Prevention Awareness Program for Black Americans:

Staff Support: Full-time staff allocated for this program are a Program Director (since July 1984), a Cancer Control Science Associate (since July 1985), and a Program Technical Assistant (since October 1985).

Fiscal Support: Fiscal support for the Minority Field Program in FY 1985 was $300,000. In FY 1986, funding will be $400,000, and in FY 1987 some $500,000 would be allocated under the budget request.

In addition the Institute is considering extending the outreach capabilities of the program in FY 1987 or 1988 depending on the quality of applications that are submitted at the time and the availability of funds at the time the project is approved by our scientific advisors.

BLACK COLLEGES

Mr. Stokes. How much was awarded by NCI to historically black colleges in 1985? What are your estimates for 1986 and 1987?

Dr. DeVita. In FY 1985, the NCI awarded $3,108,000 to institutions among the Historically Black Colleges. This includes research grants, fellowship awards and contracts. For FY 1986 and FY 1987, the NCI would estimate that awards to this group of institutions would remain reasonably stable.

TRAINING FOR MINORITIES

Mr. Stokes. What is your Institute doing to increase the number of minorities supported through institutional training grants that go to non-minority institutions?

Dr. DeVita. NCI is utilizing several approaches to realizing this objective.

- Consistent with NIH policy, the NCI's Cancer Research Manpower Review Committee will evaluate, in the course of its initial merit review of each NCI institutional training grant application (T32), both (a) the historical trainee population and (b) the plan for recruitment and selection of trainees during the period for which grant support is requested. An Administrative Note addressing these considerations will be included in the formal summary statement documenting the review. Concerns in this regard will be brought to the attention of the National Cancer Advisory Board.

- NCI also awards additional training slots to ongoing training programs for the sole purpose of recruiting minorities through the NRSA research training grant mechanism.

- Some time ago, through the combined efforts of the Institute's Cooperative Minority Biomedical Program (CMBP) and the Cancer Training Branch, we communicated directly to the program directors of all currently active NCI training grants regarding the opportunity for recruitment of highly qualified minority candidates, particularly for predoctoral training, from among the minority institution-based MARC Honors Undergraduate Training Programs administered by the

NIGMS. Simultaneously, we sent corresponding letters to the Directors of each of the MARC Training Programs. In this case, we provided a computer listing of all active NCI training grants, names and telephone numbers of program directors.

- Finally, we have begun to identify shortage categories in which the development of manpower in the minority communities represents an especially critical need (e.g., epidemiology, cancer control). Where the Cancer Institute is funding a training grant at a non-minority institution which has an exceptionally strong training activity in any of those areas, our program staff are encouraged to facilitate effective liaison between the minority candidate pool and the indicated NCI training program.

PROGRAM GOALS

Mr. Stokes. Dr. DeVita, do you establish goals for your senior administrators for addressing minority program and personal issues? If not, why not?

Dr. DeVita. Program goals have been established to address the problem of cancer in minorities which in particular is higher than the general population for blacks. This has led to the start of a number of initiatives to include a detailed report outlining cancer experience in blacks, a clinical trials smoking cessation study in blacks, an avoidable mortality study which concentrates on studying how to reduce incidence and mortality in the black community, increased funding to the Surveillance, Epidemiology and End Results program, to obtain more statistical information on cancer incidence and mortality of blacks and finally, a cancer center planning grant was awarded to a minority institution to foster additional research in the black community. With regard to personnel issues, the senior staff has been and continues to give increased emphasis to improving the recruitment of minorities in both scientific and administrative positions.

Mr. Stokes. How do you hold your senior officers accountable for meeting those goals?

Dr. DeVita. The staff is held accountable based on the programs which are started to deal with the cancer incidence and mortality in the minority community. These programs will be evaluated as to their effectiveness. Senior staff and I review on a bi-annual basis the progress we are making for the recruitment of minorities in terms of the number of appointments that are made in that period of time. In this way, my senior staff is accountable to me for the progress in both of these areas.

Mr. Stokes. For the record, please supply the following information for SES positions, senior level administrative positions and senior level professional positions in your Institute: the number of all such positions and the current number of these positions occupied by blacks?

Dr. DeVita. In response to your questions, the following is provided:

	Total NCI	Number of Blacks
Senior Executive Service	25	1
Senior Level Administrative	341	7

LUNG CANCER

Mr. Stokes. Dr. DeVita, I understand that only 13 percent of lung cancer patients live five or more years after diagnosis. Why is the survival rate so low?

Dr. DeVita. Lung cancer is one of the most difficult cancers in which to achieve long-term survival. The most recent data from the SEER program indicate that the survival is increasing slightly, to about 15 percent. In fact, about half of all lung cancers are not operable when the patient is first seen by the physician. These patients are often diagnosed to have metastatic disease with a very poor prognosis. Of the remaining 50 percent of lung cancer patients about half, or 25 percent have cancers that while operable are not resectable, either because of the particular nature of the cancer, or the degree to which it has spread.

Of the remaining 25 percent of all patients about 40 percent (or 10 percent of all patients) are found to have disease that does not respond positively to treatment. The remaining 15 percent of all patients, about 20,000 persons annually, do respond to treatment and in fact represent patients who can be cured of the disease.

In essence, we encounter the disease at too late a stage to affect its ultimate course. But lung cancer is mainly due to cigarette smoking -- some 85 percent of the disease is attributable to this cause -- and because of this fact it can be greatly reduced. We have seen a downturn in lung cancer incidence in white male adults. However, the rates continue to climb in women and adolescents as they continue to smoke at an early age. These trends have set the goals for the NCI smoking program to address those groups at the highest risk.

Mr. Stokes. What are the recent trends with respect to women and lung cancer?

Dr. DeVita. The age-adjusted incidence rates for lung cancer among black and white women have been increasing at an annual rate of six percent during the 10-year period of 1974 through 1983. The incidence rates for women of both racial groups are nearly identical. The 1983 incidence rates were 33.5 per 100,000 for white women and 33.9 for black women.

The same trends are seen for lung cancer mortality among women as are seen for incidence. Lung cancer mortality rates among white women increased by 5.8 percent per year from 1974 to 1983 with rates of 14.3 per 100,000 and 24.5 respectively. The rates for black women increased from 14.1 in 1974 to 24.8 in 1983, an average annual rate of increase of 6.2 percent per year.

We believe that these rates are increasing because women have not quit smoking as rapidly as men during the last 20 years. The smoking prevalence rate for men in the United States dropped from 52 percent of adults in 1965 to 32 percent in 1983. During this same time period the smoking prevalence rates for women only decreased by five percentage points, from 34 percent in 1965 to 29 percent in 1983.

CONSORTIUM OF MINORITY MEDICAL SCHOOLS

Mr. Stokes. I understand that there is a cancer center application from the consortium of minority medical schools. Will this center application be funded, given cutbacks in the cancer center program?

Dr. DeVita. The cancer center application from Charles R. Drew Postgraduate Medical School for a planning grant to create a consortium of black schools (Drew, Meharry Medical College, and Morehouse School of Medicine) has been reviewed.

It received a fundable priority score and should be funded from the cancer center budget in FY 1986.

CLINICAL TRIALS

Mr. Early. Are there any high-priority clinical trials which are ready but cannot be initiated because of lack of funds in the FY 1987 request? If so, please provide a list of these, along with a brief description and the associated costs, including first year costs.

Dr. DeVita. There are a number of high-priority clinical trials which cannot be initiated because of the funding in the FY 1987 request.

	(In Thousands) Cost	
	1st Year	Total
Treatment of Medulloblastoma: Medulloblastoma is a cerebellar tumor which is more often seen in children than in adults, and has been shown to be highly radiosensitive. A clinical trial will evaluate the effectiveness of postoperative radiotherapy and adjuvant chemotherapy in children with this cancer.	$ 100	$ 300
Study of Photodynamic Therapy in Treatment of Bladder Cancer: Cells which have been exposed to hematoporphyrin are easily destroyed by exposure to laser light; tumor cells take up this compound much more quickly than normal cells. This therapy appears to be promising for the treatment of superficial cancers of the bladder and some other sites.	70	210
Use of Tumor Necrosis Factor (TNF) in Metastatic Cancer: TNF is a biological response modifier which has shown promise in laboratory animals and in preliminary clinical studies. Additional clinical studies of TNF in patients with metastatic cancer who have failed conventional therapies will allow a more rapid accrual of research data.	1,150	3,450
Use of Labelled Antibodies to Detect Hodgkin's Disease Involvement: This study would utilize radiolabelled monoclonal antibodies to detect sites of Hodgkin's Disease involvement in a study to develop a better prognosis indicator of treatment progress.	182	546
Biochemical Modulation of Chemotherapeutic Agents: Numerous preclinical studies have shown improvement in the therapeutic index of currently available drugs when biochemistry and pharmacology are exploited to modulate their action. Several studies are underway; additional studies would involve colorectal, breast, stomach, and head and neck cancer.	750	2,200
Phase II/III Clinical Trials Using Hyperthermia: Hyperthermia, the application of heat to tumors, would be investigated. Evidence exists that carefully applied heat, in conjunction with other	600	1,800

	(In Thousands) Cost	
	1st Year	Total
therapies, can be effective in treating cancers in locations such as limbs, which can be selectively exposed to heat.		
Phase I/II Trials of Additional Biological Response Modifiers: Research is continually uncovering previously unknown biological response modifiers which, after initial characterization, can be entered into clinical studies for efficacy studies.	6,000	8,500
Treatment of Metastases with Surgery Followed by LAK Cells/IL-2 Therapy: The effectiveness of LAK cell/IL-2 adjuvant immunotherapy for treatment of resectable colorectal/hepatic metastases following surgery would be undertaken.	575	1,725
Phase III Studies of Adoptive Immunotherapy of Cancer with Autologous LAK Cells and IL-2: These national scale trials would involve approximately 500 cancer patients and provide definitive data on the effectiveness of this promising new treatment approach. It should be noted that changing technology may affect the cost of this investigational treatment.	20,000	40,000
TOTAL UNFUNDED CLINICAL TRIALS	$29,427	$58,731

ADDITIONAL FUNDS

Mr. Early. If an increase over the FY 1987 request is provided, how would you use these additional funds?

Dr. DeVita. As I have previously mentioned, the resources provided with the President's request will permit the Institute to support its highest priority research efforts. However, as is the case with most program administrators, additional resources could be used to further enhance or implement initiatives. Dependent on the level of increase over the President's Budget, additional effort in prevention, treatment and basic research would be supported. Funds would be utilized to restore or expand ongoing initiatives as well as initiate new research opportunities. The Institute continues to consider the support of basic research as its highest priority. It is important to consider that support of basic research is not accomplished through research grants alone. Many of the current exciting opportunities in cancer research have originated from basic research efforts supported through other mechanisms - most notably intramural research, research and development contracts, prevention and cancer control activities, and centers. Since all of these mechanisms are important to the cancer continuum any expanded funding would be distributed to take advantage of the most exciting research opportunity regardless of the support mechanism.

FY 1987 REQUEST

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed by lack of funds in the FY 1987 budget?

Dr. DeVita. Again, we will continue to support the highest priority research efforts within the levels provided in the President's request. There are, of course, additional new initiatives that could be funded, if additional resources were provided. We would first consider the total amount of additional resources and ascertain the appropriate amount required for restoration or expansion of ongoing initiatives vis a vis to the level for new efforts. Some of the new initiatives that could be supported include:

- A contract initiative for the development and operation of a high-capacity prescreen for development of cancer effective drugs ($2.5 million);
- Phase I/II and Phase II/III clinical trials for a national effort in lymphokine-activated killer (LAK) cells and Interleukin-2 (IL-2) therapy ($20.0 million);
- Establishment of additional cancer information initiatives directed toward minority population ($2.0 million);
- An expanded Community Clinical Oncology Program for greater geographic and demographic dispersion ($4.0 million);
- Epidemiologic efforts including those within the SEER program as well as computerized enhancement of information dissemination activities ($5.5 million);
- Cancer control initiatives including pain control, role of primary care providers in health promotion, training of scientists with a high level of cancer control expertise and programs dealing with the continuing care of cancer patients ($3.0 million);
- Diagnostic research efforts including cytogenetic applications to diagnosis, prognosis and risk assessment and establishment of a human tissue network ($2.0 million); and
- Clinical trials, including chemoprevention trials ($6.0 million).

Mr. Early. Doctor, will any significant research initiative currently underway be halted or seriously delayed due to FY 1987 funding levels?

Dr. DeVita. In constructing the FY 1987 budget, hard decisions had to be made in regard to the funding of many competing priorities. The Institute will always seek to fund the highest priority research, and as such, no significant initiative will be halted or seriously delayed.

Mr. Early. To what extent will there be major reductions in the scope of ongoing or new initiatives because of the FY 1987 funding levels? For the record, provide a list of these along with a brief description and the amounts associated with each initiative.

Dr. DeVita. As mentioned earlier, the Institute will attempt to protect the areas which have the highest potential for payoff in terms of curing cancer. However, it is important that the Institute remain flexible in order to be able to react promptly through the redirection of resources, in order to maximize on the taxpayers investment in cancer research. Ongoing initiatives that will be affected follow:

- Reductions below recommended levels for all grant-supported programs ($62.0 million);

- Elimination of the construction program at the FY 1986 level ($6.5 million);

- Indicative of the kind of basic studies to be slowed are research on how the stages of carcinogenesis induced by chemical or physical agents are regulated; diagnostic activities as they relate to cancer, specifically research on the applications of recombinant DNA technology; research on monoclonal antibodies and immunotoxins; research on applications of recombinant DNA technology to cancer diagnosis, cytogenetics and predisposition to cancer; a contract providing for the acquisition, cataloging, storage, and maintenance of cell lines which are capable of long-term growth *in vitro* and are useful in tumor immunology and in tumor diagnosis; studies of how the stages of carcinogenesis induced by chemical or physical agents are regulated; studies on the chromosomal regulation of cytochrome P450 genes; and studies on applying the transgenic mouse system to introduce specific genes into the germline of the murine genome, including the expression, interaction, with chemical carcinogens, and the biological consequences of the introduced genes in the host animal throughout development ($4.0 million);

- Treatment research studies in pharmacokinetics, drug development, and animal studies ($3.0 million);

- Prevention initiatives including collaborative agreements with the EPA and NIOSH for research on environmental and occupational cancers; NCI-minority focused initiatives, the Comprehensive Minority Biomedical Program (CMBP) would delay the initiative of implementing additional satellites to stimulate the entry of minority populations into active research protocols. The level of co-funding of MARC/MBRS grants would be reduced; and several initiatives in smoking research will be delayed. Among those requiring additional funds are the prevention and cessation of smokeless tobacco; smoking prevention and cessation among women; and intervention studies directed toward heavy smokers including blacks and Hispanics ($14 million).

- Information Dissemination activities via publication and promotion will be reduced in scope to include: patient education programs directed to physicians and other health professionals who help cancer patients; and programs in the areas of smoking, diet and cancer, and other areas of cancer risks ($7.0 million).

ADJUVANT CANCER THERAPY

Mr. Early. This year we have heard a lot about adjuvant breast cancer therapy. Can you tell us more about the disease and adjuvant cancer therapy? Does it only apply to breast cancer? How many deaths might be prevented if patients were offered this treatment option?

Dr. DeVita. Breast cancer is one of the most important causes of cancer death in American women. Each year in the United States, this disease is diagnosed in approximately 130,000 women and causes 30,000 deaths. Overall, about one American woman in 14 will develop breast cancer during her lifetime, and the incidence of this disease is expected to increase in the future. For this reason, treatment research in breast cancer is an important priority at the NCI.

Cancer physicians have recognized that surgical removal of the breast cancer was unlikely to be curative for women in whom regional lymph nodes were found to be involved with tumor. At the time of critical surgery, such women eventually developed distant tumor spread, or metastasis. Adjuvant therapy is treatment with chemotherapy, biological agents, hormones or radiation given immediately after surgery to high-risk patients in an effort to lessen the chance of disease recurrence. The hypothesis of adjuvant therapy is that this treatment will improve survival in such high-risk patients as women with breast cancer who had initial lymph node involvement.

Today, there is no controversy as to the essential correctness of the hypothesis of adjuvant chemotherapy. The effectiveness of adjuvant therapy has been proven in women with breast cancer, in patients with bone tumors (osteosarcoma), solid tumors of childhood, and in rectal cancer. Clinical research in breast cancer has allowed physicians to predict with increasing accuracy and sophistication which individual patients are most likely to benefit from adjuvant treatments. For example, an International Consensus Conference on adjuvant therapy of breast cancer held at the NIH in September of 1985, concluded that chemotherapy was effective treatment for premenopausal breast cancer patients with cancer-involved lymph nodes, while hormonal therapy with an antiestrogen (tamoxifen) is effective for postmenopausal patients with positive lymph nodes. When combined with radiation or surgery, such therapy results in a 25 percent reduction in overall death from disease in high-risk patients.

In addition, other common cancers of adults are susceptible to the adjuvant therapy approach. Last year, an important study was reported in which therapy consisting of 5-fluorouracil and a biological agent (levamisol) improved survival for patients with Stage C colon cancer. Again, this positive finding holds the promise of saving over 8,000 lives in the United States each year. This study is now being confirmed in a large national trial supported by the National Cancer Institute.

The Gastrointestinal Tumor Study Group has recently demonstrated improved survival for patients with rectal cancer undergoing adjuvant chemotherapy (5-fluorouracil and methyl CCNU) and with radiotherapy. With a 20 percent improved survival rate for treated patients, this trial could save the lives of 4,000 Americans each year if applied on a national scale. In a study by the Lung Tumor Study Group released this year, one major form of cancer of the lung that is one of the most difficult cancers to treat has shown positive results in adjuvant therapy trials.

In toto, the results of positive adjuvant therapy trials in breast, colon, rectal, and lung cancer and in the sarcomas (tumor of muscle, bone and connective tissue) could save more than 22,000 lives each year if applied at the community level.

Mr. Early. How many adjuvant clinical trials are you supporting? Do you anticipate any cutbacks in this area?

Dr. DeVita. The present challenge for clinical research is to make adjuvant therapy more effective with fewer side effects. Currently, Clinical Cooperative Group adjuvant studies are ongoing or scheduled to begin this year in the following areas: for pediatric patients -- osteosarcoma, Ewing's sarcoma, Wilm's tumor, lymphoma, and neuroblastoma; for adult patients -- early stages of testis (seminoma) tumor, osteosarcoma, lymphoma, bladder, cervix, stomach, pancreas, liver, prostate, head and neck and melanoma (a form of skin cancer). The efforts in breast, colorectal and lung cancer will continue.

These studies represent an area of important promise for patients with common cancers and are of the highest priority to the clinical trials program. If significant resource cutbacks are required, redistribution of resources may be necessary to continue support of adjuvant therapy clinical studies.

COMMUNITY OUTREACH ACTIVITIES

Mr. Dwyer. How would you assess the availability of the state-of-the-art treatments developed through NCI-supported research for cancer patients in communities across the country?

Dr. DeVita. Effective treatments are available from community medical providers for a number of cancers as a part of good oncology practice. These treatments have frequently been developed through NCI-supported research and disseminated through papers in professional journals, the educational efforts of professional societies and through training offered in medical schools.

For cancers for which effective treatments are not yet available the opportunity to participate in clinical research is available in every state, except Alaska. In addition to the cancer centers, clinical research protocols are utilized in approximately 290 Clinical Cooperative Group member institutions primarily located at universities and in approximately 950 community locations (750 Cooperative Group Outreach Program affiliates, and more than 200 Community Clinical Oncology Program participating hospitals).

Information on state-of-the-art cancer treatment is also available through the PDQ, a nationwide computer based cancer information service. Medical libraries and doctors with their own computers can have access to the data, including current reports on the ongoing experimental therapies.

Mr. Dwyer. What impact will the reductions requested for the cancer prevention and control programs have on the Community Clinical Oncology Program (CCOP) and the Cooperative Group Outreach Program (CGOP) which have helped community-based physicians make new treatment approaches more accessible to cancer patients?

Dr. DeVita. Currently funded programs should still operate effectively, albeit at a moderately reduced rate. Some of this reduction will result from the deficit reduction requirements, but some will be due to a readjustment of program strategies to continue to meet the management needs of cancer patients throughout the nation. The importance of helping community-based physicians provide the latest state-of-the-art procedures is a major component of the NCI's year 2000 plan. The way to accomplish that, however, is not necessarily monolithic. Following evaluation of the CCOPs, it is entirely feasible that additional and perhaps more effective strategies (modified CCOPs) will be implemented along with other variations of the CGOP.

Mr. Dwyer. If additional resources were available for these two programs, what types of activities could be funded?

Dr. DeVita. It is anticipated that cancer prevention and early detection activities and cancer control research not currently funded could be included as part of the programs. These community groups lend themselves nicely to chemoprevention and detection studies aimed at preventing cancer incidence and increasing survival respectively.

COMMUNITY ONCOLOGY PROGRAM

Mr. Dwyer. Please elaborate on the early case detection studies for high-risk groups which you mention in your justification. What emphasis is being placed on geographic areas of the country with high rates of cancer and identifying those environmental factors that might contribute to high influence in certain parts of the country?

Dr. DeVita. The entire country is being monitored for cancer death rates. These rates are being evaluated utilizing detailed maps of counties demonstrating low, medium and high mortalities.

In 11 areas where there are SEER programs incidence and stage of disease (indicating early or late detection) are available for monitoring high incidence levels in 12 percent of the U.S. population. Over half of the states have incidence cancer registries. These registries are presently being evaluated as possible resources for identifying high-risk groups, as well as patterns of care and delivery of state-of-the-art treatment.

INTRAOPERATIVE RADIATION THERAPY

Mr. Dwyer. What findings can you report on the effectiveness of Intraoperative Radiation Therapy (IORT), a technique which uses highly specialized equipment to irradiate exposed tumors without damaging surrounding tissues? Do you anticipate any curtailment in the level of support for centers which are testing this promising technique, as a result of your FY 1987 budget request?

Dr. DeVita. Intraoperative radiation therapy continues to be a promising cancer treatment technique in that it utilizes radiation beams, generally electrons, which are given at the time of surgery to a tumor exposed by surgical techniques. This allows treatment of the tumor and sparing of the normal overlying tissues which could be adversely affected by radiation beams, particularly those used in high doses. Several early studies designed to determine toxicities and efficacy have been done on cancers of the stomach, pancreas and connective tissues of the abdomen. Disease in which improvements in patient survival have been shown include stomach cancer and retroperitoneal sarcoma (cancer of connective tissues of the abdomen), and early data suggest that similar improvement may occur in pancreatic and rectal cancer as well. Toxicities primarily result from damage to nerves in the irradiated area. Six separate disease sites are proposed for study in clinical trials by the Radiation Therapy Oncology Group (RTOG) to determine how efficacy may be enhanced. These include stomach, pancreas, bile duct, rectum, sarcoma and cervix. It is anticipated that more advanced trials utilizing this therapeutic modality will be developed in the near future.

With regard to support for testing this promising technique, clinical studies at three institutions have been supported by contracts in this investigational area and have reached completion. These institutions are the Mayo Clinic, Howard University, and Massachusetts General Hospital. Currently, a supplemental grant to the Radiation Therapy Oncology Group to support further clinical studies is being reviewed.

FY 1987 REQUEST

Mr. Hoyer. Dr. DeVita, what is your budget request for the Institute for FY 1987 to Dr. Wyngaarden?

Dr. DeVita. The National Cancer Institute's FY 1987 preliminary budget request to NIH was $1,463,191,000.

Mr. Hoyer. How much did NIH request?

Dr. DeVita. NIH submitted its FY 1987 request to PHS at an aggregated level, or total NIH, rather than by individual Institute.

Mr. Hoyer. What was the PHS request to the Department?

Dr. DeVita. Again, PHS submitted an aggregated NIH mechanism table to the Department. I can tell you that the Department forwarded a request in the amount of $1,345,058,000 to OMB for the National Cancer Institute for FY 1987.

Mr. Hoyer. How would you have used the extra money?

Dr. DeVita. The increased funding would have gone into the support of additional research project grants, one of the primary areas where basic cancer research is supported; funds would have been provided to support cancer centers at recommended levels, as well as increase the number of centers. Shared equipment at existing centers would have been upgraded to more state-of-the-art capability; clinical cooperative agreements would have been funded closer to full funding levels and activities expanded as well; for all other research grants, the level of effort supported would have been expanded. Within research and development contracts additional support would have been provided to capitalize on the many opportunities available for exploitation, including drug development activities, and the role of magnetic resonance imaging versus computerized tomography scanning in diagnostic imaging of diverse organ-specific disease. Intramural efforts would have been expanded and funds provided to support additional staff. Construction funding was provided to upgrade, modernize and maintain both extramural and intramural cancer research facilities.

DIAGNOSTIC RELATED GROUPS

Mr. Hoyer. Dr. DeVita, last year I asked you what effect DRG(s) were having on cancer centers. You expressed concern that it might decrease the patients who will go on clinical trials. You continued by stating that you were evaluating the effects and that this review might take a year or so.

Is there anything that you can share with this Committee on this subject?

Dr. DeVita. The NCI/NCHR study of the effect of DRGs on clinical research is in progress at this time. In addition there are other studies being conducted by other institutions in the

United States attempting to determine what effect DRGs have on clinical research both in cancer centers and universities. At this time, we cannot give you definitive information with regard to this question.

PDQ SYSTEM AND THE INTERNATIONAL CANCER INFORMATION BUDGET

Mr. Hoyer. I am a strong believer that the dissemination of information, regarding the findings at NCI, is vital in our battle against cancer. In this regard, what is the budget request for the International Cancer Center?

Dr. DeVita. The budget request for the International Cancer Information Center for FY 1987 is $7.8 million.

Mr. Hoyer. What is the budget for the PDQ system?

Dr. DeVita. The International Cancer Information Center's FY 1987 program costs for PDQ operations amounts to $2.2 million.

Mr. Hoyer. Are any new initiatives or expansion of ongoing activities planned in FY 1987?

Dr. DeVita. The International Cancer Information Center currently has no plans for new initiatives or expansion of ongoing PDQ activities in FY 1987. There are however, in various stages of planning, several developments, e.g., a prevention file (PDQ-P), that will be added to the system in order to increase its applicability even further.

Mr. Hoyer. Last year, you stated that you signed a licensing agreement with BRS/Saunders and the Hospital Satellite Network.

What has been the response to this effort?

Dr. DeVita. To date, two American database vendors have signed license agreements with NCI, and the PDQ database is now an integral component of two on-line medical information systems that are being marketed to the medical community: the COLLEAGUE system produced by BRS/Saunders and the MEDIS system produced by Mead Data Central. Each vendor rebuilds the entire PDQ database each month with a replacement distribution tape that is supplied by NCI as part of the lease agreement. The vendors are free to modify the presentation of the data as long as they convey the information with its original meaning intact.

CANCER INCIDENCE IN THE POPULATION

Mr. Hoyer. Is the incidence of cancer in the general population increasing or decreasing?

Dr. DeVita. The incidence rates for all cancer sites combined have shown small increases within each race-sex group for the last 10 years. The incidence rates for white males increased from 372.8 per 100,000 in 1974 through 1975 to 401.7 in 1982 through 1983, an average annual increase of 0.8 percent; the rates for white females increased by 0.1 percent per year during this same time period, 309.2 per 100,000 to 311.4. The rates for blacks also increased:

1.8 percent per year for black males, from 426.6 per 100,000 to 505.2; and 0.4 percent per year for black females whose incidence rates increased from 286.8 per 100,000 in 1974 through 1975 to 297.9 in 1982 through 1983.

We believe that it is also reasonable to analyze cancer incidence trends for all sites with the exception of lung cancer. Lung cancer has been increasing in all race-sex groups until 1983 when for the first time in a half century it decreased four percent for males. The incidence rates for white males increased from 298.2 per 100,000 in 1974 through 1975 to 320.7 in 1982, an increase of 0.8 percent per year. This increase is primarily due to cancer of the prostate. The incidence rates for white females when lung is subtracted show decreases, from 288.5 to 278.1, a yearly decrease of 0.4 percent per year. Cancer incidence rates for all sites minus lung among black males also increased during this 10-year period. Among black males, the incidence rates increased by 1.7 percent per year from 326.2 per 100,000 in 1974 through 1985 to 381.1 in 1982 through 1983. The trends in cancer incidence for all sites minus lung among black females was level at an annual rate of 266 per 100,000 black females during this 10-year period.

CANCER TREATMENTS

Mr. Hoyer. Is the Nation spending more or less on cancer treatments this year as compared to one or two years ago?

Dr. DeVita. Because the increase in medical care costs each year continues to exceed the overall national rate of inflation, the Nation is spending more on cancer treatments this year as compared to one or two years ago. A study by the National Center for Health Statistics (NCHS) puts overall medical care for cancer at $10.8 billion for 1980. That figure could easily have increased by now.

Mr. Hoyer. In the area of cancer treatment you mentioned a promising trial using adoptive immunotherapy.

What is the most promising development in cancer immunology?

Dr. DeVita. The most promising development in cancer immunology has been adoptive immunotherapy. This new therapy combines an immune system activator, Interleukin-2 (IL-2), with a unique population of immune cells known as lymphocyte activated killer cells (LAK). In order to generate the LAK cells, white blood cells are removed from the patient and exposed to IL-2 in culture in the laboratory. This treatment causes the proliferation of a population of cells (LAK cells) which are able to recognize and kill human tumors. These LAK cells are reinfused into the patient and the patient is also given systemic IL-2 at the same time. The IL-2 induces the LAK cells to multiply for a short time in the body, thus enhancing their ability to destroy cancer cells. Dr. Rosenberg reported the results of the first 25 patients treated in this way in December 1985 issue of the New England Journal of Medicine.

As of February 20, 1986, 49 patients have been treated by Dr. Rosenberg and 18 (37 percent) had either a partial or complete remission. Additionally, six patients have been treated in the Biological Response Modifiers Programs at the Frederick Cancer Research Facility and two of the patients have had a response. The toxicities of this treatment, primarily to the high doses of IL-2, are significant and include fluid retention, low blood pressure, and acute renal failure. These toxicities are reversible but highlight that this experimental therapy must be tested in carefully controlled clinical trials in order to determine both its effectiveness and means of decreasing the toxicity.

This therapy is most active in colorectal carcinoma, renal cell carcinoma, and melanoma (a form of skin cancer). These tumors account for approximately 160,000 cases of cancer and 72,000 cancer deaths each year. Investigators at Massachusetts General Hospital treating patients with adenocarcinoma of the lung are using a similar technique whereby T-cell lymphocytes obtained from the patient's tumor are propagated with IL-2 and reinfused into the patient with IL-2. The initial results look promising. Adenocarcinoma of the lung accounts for 30,000 cancer deaths each year.

Six other centers have been chosen to confirm the results of Dr. Rosenberg's trial and will begin treating patients soon. These include: Tufts New England Medical Center, Boston; City of Hope, Duarte, California; Loyola University, Maywood, Illinois; University of California at San Francisco; University of Texas Health Science Center, San Antonio, and Montefiore Hospital, Albert Einstein Medical School, New York. Additionally, the University of Wisconsin has begun a trial using this technique.

SURVEILLANCE, EPIDEMIOLOGY AND END RESULTS PROGRAM (SEER)

Mr. Hoyer. How does the SEER program differ from the 34 intervention studies that NCI will be conducting in FY 1987?

Dr. DeVita. The SEER program is a population based minority system which allows NCI to measure the cancer burden in the United States. The intervention studies are studies which are designed to reduce the cancer burden. Thus, the SEER program will be one of the tools whereby the success of these proposed interventions can be measured.

Mr. Hoyer. How much will be spent on each activity?

Dr. DeVita. In FY 1987, the budget for the SEER program (which monitors cancer patient treatment and survival as well as measuring the cancer burden in the U.S.) is $10.3 million. The amount allocated for intervention studies totals $32.3 million and is distributed among the different areas of intervention as follows:

	(In Millions)
Smoking, Tobacco & Cancer	$12.6
Chemoprevention	7.0
Diet & Nutrition	1.4
Cancer Control Applications	9.7
Health Promotion Sciences	1.6
Total	$32.3

NURSING POSITIONS

Mr. O'Brien. Last year, you told me that "The implementation of well-designed clinical trials in cancer treatment is feasible only with a cadre of dedicated and specially trained oncology nurses. At present, optimal nursing care would require 20 additional nurses over current staffing levels provided by the Clinical Center."

And later, you said, "The Secretary has directed NIH to give priority recruitment to those positions involving direct patient care."

My question, now Dr. DeVita, is whether or not those nursing positions have been filled, and whether or not, the Clinical Center is fully utilized at the present?

Dr. DeVita. Last year, I testified that an additional 20 nurses over current staffing were required. Subsequent to that testimony, 10 additional nursing slots were allocated by the Director, NIH, to the Cancer Nursing Department for our adult Medical Oncology Program located on 13 East and 13 North Corridors of the Clinical Center. Currently, 20 of the 40 beds on that unit remain closed because of an inability to recruit or redistribute nursing personnel to the Clinical Center's busiest wards. Our recruitment and retention of nurses has been difficult as a result of the salary levels for Government nurses. Furthermore, when one adds the additional demands of caring for cancer patients to the low pay scale, our recruitment and retention problem becomes even more acute.

Mr. O'Brien. Dr. DeVita, what was the direct impact in your Institute -- on nursing positions, on other positions -- of the March first Gramm-Rudman sequestration?

Dr. DeVita. The Gramm-Rudman-Hollings sequestering had no direct impact on full-time equivalents (FTEs). Policy decisions used in deriving the President's FY 1987 budget mandated some reductions to staffing levels.

As previously mentioned, 10 additional nursing slots were allocated last year by the Director, NIH, to the Cancer Nursing Department for NCI's Medical Oncology Program located in the Clinical Center. This represented half of the total additional requirement for nursing positions. The recruitment and retention of nurses at the Clinical Center has been difficult as a result of non-competitive salary levels for Government nurses. However, redistribution of nursing FTEs to the busier cancer wards is a possibility that can be considered.

CANCER INCIDENCE IN THE POPULATION

Mr. O'Brien. Last year, you pointed out in material supplied to the Committee that the growth of cases is directly related to population growth and the relative increase in the number of older Americans. You stated that half of all cancer occurs in persons over the age of 65.

What specific research is being conducted at the Institute dealing with the aging population and the incidence of cancer?

Dr. DeVita. The NCI is supporting studies on patterns of care for elderly cancer patients, taking into account the many factors that contribute to health status, well-being, and effective patient care. The aim is to increase the knowledge base on cancer-related problems unique to older-aged persons. The research scope of cancer in the elderly includes studies on elderly patients with lung, breast, prostate, cervical, colorectal, and other cancers where age, physical performance, treatment toxicity, medical management, health care utilization, psychosocial and emotional influences, and economic factors are the parameters of interest.

Mr. O'Brien. Is the incidence of cancer in the population, under age 65, continuing to decline? You indicated last year that such was the case. Please provide for the record a chart that shows the trends regarding the incidence of cancer in the various age groups of the country.

Dr. DeVita. The table below gives cancer incidence rates for all sites combined, for all races and for both sexes over the 10-year period 1974 though 1983. These rates are from the SEER program that monitors about 10 percent of the United States population for cancer incidence and survival. The age-adjusted incidence rates for ages zero to 64 has decreased by 0.2 percent per year from 1974 through 1983 from a rate of 181.5 cases per 100,000 population in 1974 to a rate of 177.6 cases per 100,000 population in 1983. If lung cancer were not included (lung cancer, the most preventable cancer is the principle reason that the rates of cancer are not decreasing further), rates would range from 156.9 in 1974 to 149.7 in 1983, an average decrease of 0.5 percent per year.

Cancer incidence rates from 1974 through 1983 by age
for Ages under 65, all races, both sexes

	Age Group						
Year	0-64	0-14	15-34	35-44	45-54	55-64	65+
1974	181.5	13.0	38.7	156.4	434.4	889.4	1,694.2
1975	179.1	11.2	39.2	154.8	417.1	892.9	1,709.6
1976	180.9	12.6	38.9	147.2	436.7	893.2	1,748.7
1977	179.0	12.5	41.0	150.9	423.4	881.2	1,760.3
1978	179.1	13.0	40.3	152.8	415.7	890.6	1,761.5
1979	177.6	13.1	40.2	145.7	416.4	885.4	1,806.5
1980	177.3	13.0	40.2	147.0	411.1	889.4	1,840.8
1981	180.5	12.3	41.1	148.2	414.9	916.0	1,868.2
1982	178.8	13.2	41.4	148.0	402.2	914.3	1,869.3
1983	177.6	13.0	41.1	153.1	399.7	900.8	1,879.3
	-0.2*	0.6*	0.7*	-0.4*	-0.8*	0.3*	1.2*

* Average annual percent change

SUPERCOMPUTER

Mr. O'Brien. What are the expected benefits of having the supercomputer capability at the NCI?

Dr. DeVita. Over the past decade we have witnessed the advent of a "biological revolution" manifested by an explosion of technology including recombinant DNA technology, gene cloning, rapid DNA sequencing, and the application of monoclonal antibodies in the detection and treatment of disease. This has led to a complex of data that, like the study of DNA previously, would seem to be impossible to fully analyze. With the rapid increase in computer technology, however, the use of supercomputers in biology brings the solution to these extremely complex problems into the realm of reality. NCI's acquisition of the supercomputer represents the only supercomputer facility anywhere dedicated solely to biomedical research. It is not possible for anyone to anticipate all the applications a supercomputer will have. However, the supercomputer will provide a milieu for the creative intellect to expand. There are, however, a number of urgent scientific problems that need the power of a supercomputer such as: nucleic acid and protein sequence analysis; x-ray crystallography in the study of the atomic structure of substances such as proteins; three-dimensional graphic analysis and molecular dynamics to help design new drugs and to study proteins; and rapid analysis of large databases of patient information, clinical data, sequence data and similar database problems.

All of these problems depend on applied and theoretical developments in numerical analysis, algorithms, geometry, statistics, and other areas of math acquiring powerful, general purpose computing. These tools are proving to be central to progress in the pursuit of solutions to cancer research problems. Oncogenes, and the subtle relationships with their non-oncogenic counterparts, are at the center of molecular cancer research. They are best defined and related to other functional genes through computerized sequence analysis. Their predicted proteins are classified by computer at a rate that would be nearly impossible by using test tube methods. Quantum chemistry calculations are being used to understand the properties of both carcinogens and anticancer drugs, and their interaction with DNA and proteins. THe supercomputer will be used for protein engineering to stimulate molecules of altered oncogenes, enzymes, antigens and antibodies on the screen of a workstation in sufficient detail that we can predict their properties before they are made by costly laboratory methods. The supercomputer will be of great value in discovering the principles of special techniques such as imaging or electronic circuit design and in stimulating their behavior prior to development of special purpose hardware. All of these tools will be of used in developing diagnostic methods, understanding the biology, improving treatment, defining the etiology, and expanding the prevention of cancer and other diseases.

PHYSICIAN DATA QUERY (PDQ) SYSTEM

Mr. O'Brien. Please provide an updated assessment of the Institute's efforts to disseminate information on cancer research and its applicability to the practicing physician -- I believe this is called the "PDQ system".

Dr. DeVita. The Physician Data Query (PDQ) system represents a major effort by the NCI to accelerate the transfer of new knowledge about advances in cancer treatment. PDQ is an essential component of the NCI's program to establish effective communication links between clinical investigators and practicing physicians. by accessing PDQ a practicing physician can readily identify those therapies that are considered to be state-of-the-art treatment for patients with cancer, as well as information on investigational treatment approaches that may benefit cancer patients in their care.

PDQ operates as an interactive database that can be accessed by multiple users simultaneously through standard communications networks on a variety of computer terminals. By design, PDQ is simple to learn and easily used even by individuals who have little or no experience with computers or searching on-line information systems. For ease in searching, the database is completely menu-driven; users are provided with menu options and prompts that specify particular data operations. This eliminates the need to remember a complex sequence of commands or to learn a specialized programming language. The system also includes "help" facilities that explain information retrieval functions to the user.

The information in PDQ is organized into four major data files: cancer information; a physician directory; an organization directory; and a protocol file that contains descriptions of active clinical research studies that are open for patient accrual. Although the records in these files can be accessed and reviewed as discrete and unrelated entities, PDQ is a system of interlinked files that is responsive to the user's desire to move quickly and easily from one file to another.

The PDQ cancer information file provides prognostic and treatment information in two formats: a "capsule summary" and state-of-the-art information. These formats are selectable options from a cancer information menu. Capsule summaries are designed to provide physicians with educational information that may be shared with patients and their families when the prognosis and treatment of the cancer is discussed. The capsule summary's brief overview on prognosis, stage, and treatment options is complemented by a more technical, detailed state-of-the-art statement which is designed to provide physicians with up-to-date medical information on the cancer and its treatment. State-of-the-art treatment statements contain explicit information on the management of patients with a particular type of cancer. The statements are concise and include a prognostic statement (an indication of the curability of the disease and determinants of cure); information on cellular classification of the neoplasm; a description of the accepted staging classification (if more than one staging system has been developed for the disease, a comment is generally made about why one has been selected over the other); survival data by stage of disease or cell type; and a description of treatment options by stage of dissemination or other important prognostic variables. For each stage, cell type, or other criterion, treatment options are grouped into two main categories: standard and investigational.

In addition to listing a range of therapeutic options considered to be standard, the statements also comment on the use of new treatments that are under evaluation in clinical research trials. If patients with a particular type or stage of cancer should be considered as potential candidates for one or more ongoing research protocols, a comment on current approaches under evaluation in research trials is included.

A two-tiered Editorial Board which is composed of 72 prominent medical, surgical, pediatric, and radiation oncologists has been established to maintain the currency and accuracy of the medical information in PDQ and to modify the content of the statements as warranted by new data. To ensure that the information in PDQ remains current, the PDQ Editorial Board surveys the cancer literature and the state-of-the-art statements each month and updates the cancer information file as warranted by advances in treatment.

The physician directory contains information on approximately 10,000 physicians who devote a major portion of their clinical practice to the treatment of cancer patients. The directory is an electronic compilation of the membership directories of 16 national medical societies established for physicians who treat cancer. Clinical investigators whose protocols are supported by NCI, as well as those who have voluntarily submitted protocols that have been accepted by the PDQ Editorial Board for inclusion in the PDQ protocol file, are also listed in the PDQ directory. Each physician's record includes full name, address, telephone number, medical specialties, and organizational affiliations.

The organization directory includes information about health care organizations and institutions at which NCI supports clinical treatment research and those with established cancer programs. Each organization record includes the address, telephone number, and the name of a person at the institution who has agreed to serve as the PDQ contact and can answer questions about the organization's cancer treatment programs and facilities. As with the physician directory, PDQ utilizes file to file linkages to automatically display all active protocols for a specific organization if requested by the user.

The PDQ protocol file currently contains information on over 1,000 active treatment protocols that are being conducted in the United States. This file contains summaries of all active clinical trials directly supported by the National Cancer Institute, as well as treatment protocols which have been voluntarily submitted for inclusion in the PDQ database by clinical investigators throughout the country. Each protocol record includes a detailed description of the objectives of the study, patient eligibility requirements, treatment regimen, details about dose and schedule of administration, and information about who is performing the clinical trial and where it is being conducted. In the future, each protocol summary will also contain detailed information on the modifications that should be made in dose and/or schedule of administration if significant toxicity to normal tissue is encountered during treatment. Information on protocols in the PDQ protocol file is updated on a monthly basis.

Since the National Library of Medicine is a well established and highly respected source of on-line scientific and medical information with a large user base at medical libraries and health care organizations worldwide, it is the ideal organization to distribute the PDQ database to the medical community. PDQ is currently available through the National Library of Medicine's computer network at almost 3,000 health care organizations in the United States. PDQ is also available on an international basis as well, through the on-line MEDLARS centers located in Canada, Colombia, France, Italy, Kuwait, Mexico, South Africa, and the United Kingdom. The PDQ system is an international resource, and distribution of PDQ tapes to other nations is expected. Individual PDQ access codes are being made available by NCI to physicians upon request.

The National Cancer Institute has always intended that PDQ be available for commercial distribution. Accordingly, PDQ distribution tapes are provided to commercial vendors of on-line information under a lease arrangement with NCI. A number of commercial database vendors, including several European organizations, have received PDQ test tapes for use in the development of retrieval software that will enable them to distribute PDQ on their computer systems. To date, two American database vendors have signed license agreements with NCI, and the PDQ database is now an integral component of two on-line medical information systems that are being marketed to the medical community: the COLLEAGUE system produced by BRS/Saunders and the MEDIS system produced by Mead Data Central. Each vendor rebuilds the entire PDQ database each month with a replacement distribution tape that is supplied by NCI as part of the lease agreement. While the tape provides inter-file linkages and textual data elements formatted for an 80-character screen, the vendors are free to modify the presentation of the data as long as they convey the information with its original meaning intact.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

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NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

For carrying out section 301 and title IV of the Public Health Service Act with respect to cancer, [$1,258,159,000] *$1,158,089,000. (Department of Health and Human Services Appropriation Act, 1986.)*

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Amounts Available for Obligation 1/

	1985	1986	1987
Appropriation......................	$1,183,806,000	$1,258,159,000	$1,158,089,000
Enacted supplemental..............	3,000,000		
Enacted administrative reduction...		-922,000	
Sequester order....................		-53,868,000	
Proposed rescission................		-6,800,000	
Subtotal, adjusted appropriation...	1,186,806,000	1,196,569,000	1,158,089,000
Real transfer to Departmental management for Mary Babb Randolph Cancer Center..		-4,500,000	
Comparable transfer to OASH for AIDS Research.....................	-26,874,000	-27,218,000 2/	
Comparable transfers for changes in Central Services financing mechanisms and formulas from:			
National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases.................	3,411,000		
National Institute of Neurological and Communicative Disorders and Stroke............	1,024,000		
National Institute of Allergy and Infectious Diseases.........	2,437,000		
National Institute of Child Health and Human Development...	2,755,000		
National Eye Institute...........	3,087,000		
Fogarty International Center.....	8,000		
Subtotal, comparable transfers.....	-14,152,000	-27,218,000	
Total, adjusted budget authority...	1,172,654,000	1,164,851,000	1,158,089,000
Unobligated balance available start of year.....................	35,000	6,714,000	
Unobligated balance available end of year.......................	-6,714,000		
Unobligated balance lapsing........	-2,239,000	-1,090,000	
Total obligations..................	$1,163,736,000	$1,170,475,000	$1,158,089,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1985 - $990,000; 1986 - $1,000,000; 1987 - $48,379,000 of which $47,379,000 is for AIDS research.

2/ Comparable AIDS transfer at the 1986 appropriation level is $28,441,000.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Budget Mechanism
(dollars in thousands)

Research Grants	1986 Appropriation 1/2/		1986 Available After Sequestering 1/3/		1986 Revised 1/3/		1987	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Projects:								
Noncompeting projects.......	2,090	$399,538	2,090	$382,336	2,090	$382,336	2,050	$381,489
Admin supplement............	(152)	6,575	(152)	6,292	(152)	6,292	(152)	6,575
Competing								
Competing renewal.........	419	98,040	419	93,834	388	91,862	456	90,692
New......................	505	77,285	505	74,121	462	69,293	418	58,378
Supplemental.............								
Subtotal, Competing.....	924	175,325	924	167,955	850	161,155	874	149,070
Subtotal, research projects	3,014	581,438	3,014	556,583	2,940	549,783	2,924	537,134
(SBIR)....................	(35)	(3,454)	(35)	(3,305)	(35)	(3,305)	(32)	(3,167)
Research Centers								
Specialized/comprehensive...	58	85,823	57	82,132	57	82,132	57	82,282
Subtotal, research centers.	58	85,823	57	82,132	57	82,132	57	82,282
Other research								
Research career programs....	122	6,907	117	6,610	117	6,610	122	6,907
Organ systems...............	1	1,000	1	957	1	957	1	800
Clinical education program..	52	4,700	52	4,498	52	4,498	33	2,400
Coop clinical research......	252	50,204	228	48,045	228	48,045	228	49,884
Minority biomedical support.	43	3,400	40	3,254	40	3,254	42	3,400
Other research related......	34	3,440	33	3,292	33	3,292	30	3,161
Subtotal, other research...	504	69,651	471	66,656	471	66,656	456	66,552
Total, research grants.......	3,576	736,912	3,542	705,371	3,468	698,571	3,437	685,968

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
CROSSWALK - 1986 Appropriation 1/
(dollars in thousands)

	MECHANISM										
	Research Grants			Training							
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Indiv. NRSA	Instit. NRSA	R&D Contracts	Intramural Research	Rsch Mgmt & Support	Cancer Prevent. & Control	Construction	Total
Research:											
Cause and prevention research......	$185,202		$1,404			$54,297	$46,671	$17,321			$304,895
Detection and diagnosis research......	43,894		20			16,618	16,000	4,223			80,755
Treatment research......	174,748		50,604			64,934	72,842	20,167	1,677		384,972
Cancer biology.......	177,594		6,016			5,657	59,334	10,085			258,686
Subtotal.......	581,438		58,044			141,506	194,847	51,796	1,677		1,029,308
Resource Development:											
Cancer centers support.......		85,823						1,189			87,012
Research manpower development...			11,607	4,626	26,212			2,518			44,963
Construction...								452		3,200	3,652
Subtotal.......		85,823	11,607	4,626	26,212			4,159		3,200	135,627
Cancer prevention and control...								3,874	62,201		66,075
Total..........	$581,438	$85,823	$69,651	$4,626	$26,212	$141,506	$194,847	$59,829	$63,878	$3,200	$1,231,010

1/ All 1986 columns reflect an enacted administrative reduction of $922,000; and a real transfer of $4,500,000 to Departmental management for the Mary Babb Randolph Cancer Center.

Training	FTTPs		FTTPs		FTTPs		FTTPs	
Individual awards								
Noncompeting...............	125	2,800	125	2,800	125	2,800	157	3,564
Competing								
Renewal....................	1	23	1	23	1	23	1	23
New........................	78	1,803	69	1,604	69	1,604	31	705
Subtotal, individual.......	204	4,626	195	4,427	195	4,427	189	4,292
Institutional awards								
Noncompeting..............	1,050	25,437	1,036	25,085	1,036	25,085	925	22,301
Competing								
Renewal...................	22	533	0	0	0	0	58	1,517
New.......................	10	242	0	0	0	0	21	500
Subtotal, institutional....	1,082	26,212	1,036	25,085	1,036	25,085	1,004	24,318
Total training.............	1,286	30,838	1,231	29,512	1,231	29,512	1,193	28,610
Research & Develop Contracts.	449	141,506	435	135,532	435	135,532	435	133,960
(SBIR).....................	(175)	(8,746)	(175)	(8,370)	(175)	(8,370)	(172)	(8,600)
					FTE		FTE	
Intramural research..........		194,847		185,704	1,517	185,704	1,517	190,291
Research Mgmt & Support......		59,829		56,911	455	56,911	455	58,129
Cancer prevention & control..		63,878		61,131	100	61,131	100	61,131
Construction................		3,200		3,114		3,114		0
Total, NCI.............		$1,231,010		$1,177,275	2,072	$1,170,475	2,072	$1,158,089

1/ All 1986 columns reflect an enacted administrative reduction of $922,000; and a real transfer of $4,500,000 to Departmental management for the Mary Babb Randolph Cancer Center.

2/ The 1986 Appropriation reflects a comparable transfer of $28,441,000 to the Office of the Assistant Secretary for Health for AIDS research.

3/ The 1986 Sequestered and 1986 Revised Estimate reflect a comparable transfer of $27,218,000 to the Office of the Assistant Secretary for Health for AIDS research; and a consultant services (Section 515 of the Treasury-Postal Service Appropriation Act, 1985) withholding of $1,090,000.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
CROSSWALK - 1986 Available After Sequestering 1/2/
(dollars in thousands)

	MECHANISM										
	Research Grants			Training		R&D	Intra-	Rsch	Cancer		
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Indiv. NRSA	Instit. NRSA	Con- tracts	mural Research	Mgmt & Support	Prevent. & Control	Constr- uction	Total
Research:											
Cause and prevention research......	$176,203		$1,343			$51,721	$44,626	$16,426			$290,319
Detection and diagnosis research......	41,720		19			17,118	15,245	4,041			78,143
Treatment research......	168,066		48,428			61,282	69,179	19,153	1,625		367,733
Cancer biology.......	170,594		5,758			5,411	56,654	9,604			248,021
Subtotal.......	556,583		55,548			135,532	185,704	49,224	1,625		984,216
Resource Development:											
Cancer centers support.......		82,132						1,137			83,269
Research manpower development...			11,108	4,427	25,085			2,411			43,031
Construction...								432		3,114	3,546
Subtotal.......		82,132	11,108	4,427	25,085			3,980		3,114	129,846
Cancer prevention and control...								3,707	59,506		63,213
Total..........	$556,583	$82,132	$66,656	$4,427	$25,085	$135,532	$185,704	$56,911	$61,131	$3,114	$1,177,275

1/ All 1986 columns reflect an enacted administrative reduction of $922,000; and a real transfer of $4,500,000 to Departmental management for the Mary Babb Randolph Cancer Center.

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NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
CROSSWALK - 1986 Revised Estimate 1/2/
(dollars in thousands)

PROGRAM ACTIVITY	MECHANISM										
	Research Grants			Training		R&D	Intra-	Rsch	Cancer		
	Research Projects	Research Centers	Other Research	Indiv. NRSA	Instit. NRSA	Con-tracts	mural Research	Mgmt & Support	Prevent. & Control	Constr-uction	Total
Research:											
Cause and prevention research......	$174,203		$1,343			$51,721	$44,626	$16,426			$288,319
Detection and diagnosis research......	41,220		19			17,118	15,245	4,041			77,643
Treatment research......	165,666		48,428			61,282	69,179	19,153	1,625		365,333
Cancer biology.......	168,694		5,758			5,411	56,654	9,604			246,121
Subtotal.......	549,783		55,548			135,532	185,704	49,224	1,625		977,416
Resource Development:											
Cancer centers support.......		82,132						1,137			83,269
Research manpower development...			11,108	4,427	25,085			2,411			43,031
Construction...								432		3,114	3,546
Subtotal.......		82,132	11,108	4,427	25,085			3,980		3,114	129,846
Cancer prevention and control...								3,707	59,506		63,213
Total..........	$549,783	$82,132	$66,656	$4,427	$25,085	$135,532	$185,704	$56,911	$61,131	$3,114	$1,170,475

1/ All 1986 columns reflect an enacted administrative reduction of $922,000; and a real transfer of $4,500,000 to Departmental management for the Mary Babb Randolph Cancer Center.

2/ 1986 Sequestered and 1986 Revised Estimate reflect a comparable transfer of $27,218,000 to the Office of the Assistant Secretary for Health for AIDS research; and a consultant services (Section 515 of the Trea y-Postal Service Appropriation Act, 1985) wit lding of $1,090,000.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
CROSSWALK - 1987 Congressional Justification
(dollars in thousands)

	MECHANISM										
	Research Grants			Training		R&D	Intra-	Rsch	Cancer		
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Indiv. NRSA	Instit. NRSA	Con- tracts	mural Research	Mgmt & Support	Prevent. & Control	Constr- uction	Total
Research:											
Cause and prevention research......	$171,219		$1,404			$50,351	$46,089	$16,670			$285,733
Detection and diagnosis research......	42,075		20			15,980	16,001	4,096			78,172
Treatment research......	160,507		50,005			61,732	71,256	20,003	1,625		365,128
Cancer biology.......	163,333		5,816			5,897	56,945	9,866			241,857
Subtotal.......	537,134		57,245			133,960	190,291	50,635	1,625		970,890
Resource development:											
Cancer centers support.......		82,282						1,183			83,465
Research manpower development...			9,307	4,292	24,318			2,506			40,423
Construction...											0
Subtotal.......		82,282	9,307	4,292	24,318			3,689			123,888
Cancer prevention and control...								3,805	59,506		63,311
Total..........	$537,134	$82,282	$66,552	$4,292	$24,318	$133,960	$190,291	$58,129	$61,131	0	$1,158,089

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Summary of Changes

1986 Current estimated obligations	$1,170,475,000
1987 Estimated obligations	1,158,089,000
Net change	-12,386,000

Increases:	1986	Change from Base
A. Built-in:		
1. Within grade increases	$93,578,000	$778,000
2. Federal Employee Compensation Fund	395,000	78,000
3. FTS rate increase	1,430,000	393,000
4. Increased costs of laboratory supplies, materials and other expenses	116,051,000	4,556,000
Subtotal		5,805,000
B. Program:		
1. Research projects:		
a. Noncompeting continuations converting from competing status	388,628,000	165,501,000
b. Competing (new, renewals and supplements)	161,155,000	149,070,000
2. Research centers:		
a. Noncompeting continuations converting from competing status	64,080,000	18,810,000
b. Competing (new and renewals)	18,052,000	15,047,000
3. Research career programs:		
a. Noncompeting continuations converting from competing status	6,088,000	543,000
b. Competing (new and renewals)	522,000	2,350,000
4. Organ systems:		
a. Competing (new and renewals)	0	800,000
5. Cooperative clinical research:		
a. Noncompeting continuations converting from competing status	38,690,000	9,748,000
b. Competing (new and renewals)	9,355,000	6,657,000

(summary of changes cont'd)

6. Minority biomedical support:		
a. Noncompeting continuations converting from competing status	3,130,000	129,000
b. Competing (new and renewals)	124,000	1,291,000
7. Other research:		
a. Competing (new and renewals)	410,000	426,000
8. Individual training awards:		
a. Noncompeting continuations converting from competing status	2,800,000	1,695,000
b. Competing (new and renewals)	1,627,000	728,000
9. Institutional training awards:		
a. Competing (new and renewals)	0	2,017,000
10. Cancer control grants:		
a. Noncompeting continuations converting from competing status	32,680,000	4,753,000
b. Competing (new and renewals)	4,561,000	7,606,000
Subtotal		387,171,000
Total increases		392,976,000

Decreases:

A. Program:

1. Research projects:		
a. Noncompeting completed or converting to competing status	388,628,000	-166,065,000
b. Competing completed or converting to non- competing status	161,155,000	-161,155,000
2. Research centers:		
a. Noncompeting completed or converting to competing status	64,080,000	-15,655,000
b. Competing completed or converting to non-competing status	18,052,000	-18,052,000

(summary of changes cont'd)

3. Research career programs:		
a. Noncompeting completed or converting to competing status	6,088,000	-2,074,000
b. Competing completed or converting to non-competing status	522,000	-522,000
4. Organ systems:		
a. Noncompeting completed or converting to competing status	957,000	-957,000
5. Clinical education program:		
a. Noncompeting completed or converting to competing status	4,498,000	-2,098,000
6. Cooperative clinical research:		
a. Noncompeting completed or converting to competing status	38,690,000	-5,211,000
b. Competing completed or converting to non-competing status	9,355,000	-9,355,000
7. Minority biomedical support:		
a. Noncompeting completed or converting to competing status	3,130,000	-1,150,000
b. Competing completed or converting to non-competing status	124,000	-124,000
8. Other research:		
a. Noncompeting completed or converting to competing status	2,882,000	-147,000
b. Competing completed or converting to non-competing status	410,000	-410,000
9. Individual training awards:		
a. Noncompeting completed or converting to competing status	2,800,000	-931,000
b. Competing completed or converting to non-competing status	1,627,000	-1,627,000
10. Institutional training awards:		
a. Noncompeting completed or converting to competing status	25,085,000	-2,784,000
11. Research and development contracts	135,532,000	-1,572,000

(summary of changes cont'd)

12. Cancer control grants:		
a. Noncompeting completed or converting to competing status..............................	32,680,000	-7,798,000
b. Competing completed or converting to non-competing status....................	4,561,000	-4,561,000
13. Construction..........................	3,114,000	-3,114,000
Subtotal.............................		-405,362,000
Total decreases......................		-405,362,000
Total, net change...........................		-12,386,000

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NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Budget Authority by Activity
(dollars in thousands)

	1986 Appropriation 1/2/	1986 Available After Sequestering 1/3/	1986 Revised 1/3/		1987 Estimate	
	Amount	Amount	FTE	Amount	FTE	Amount
Research:						
Cause & prevention rsrch.	$304,895	$290,319	674	$288,319	674	$285,733
Detection & diagnosis rsrch..	80,755	78,143	118	77,643	118	78,172
Treatment research.........	384,972	367,733	715	365,333	717	365,128
Cancer biology..........	258,686	248,021	394	246,121	394	241,857
Subtotal..........	1,029,308	984,216	1,901	977,416	1,903	970,890
Resource Development:						
Cancer centers support..........	87,012	83,269	14	83,269	14	83,465
Research manpower development......	44,963	43,031	4	43,031	4	40,423
Construction......	3,652	3,546	2	3,546	0	0
Subtotal..........	135,627	129,846	20	129,846	18	123,888
Cancer prevention and control......	66,075	63,213	151	63,213	151	63,311
Total obligations......	1,231,010	1,177,275	2,072	1,170,475	2,072	1,158,089
Unobligated balance available start of year...	-6,714	-6,714		-6,714		
Unobligated balance lapsing..	0	1,090		1,090		
Total, budget authority........	1,224,296	1,171,651	2,072	1,164,851	2,072	1,158,089

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2/ The 1986 Appropriation reflects a comparable transfer of $28,441,000 to the Office of the Assistant Secretary for Health for AIDS research.

3/ The 1986 Sequestered and 1986 Revised Estimate reflect a comparable transfer of $27,218,000 to the Office of the Assistant Secretary for Health for AIDS research; and a consultant services (Section 515 of the Treasury-Postal Service Appropriation Act, 1985) withholding of $1,090,000.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Crosswalk - Research Programs
(dollars in thousands)

Fiscal Year 1986
Revised Estimâte

Research Programs	Cause & Prevention Research	Detection & Diagnosis Research	Treatment Research	Cancer Biology	Total
Epidemiology..............	$50,682	$13,982	$1,481		$66,145
Carcinogenesis (physical & chemical)....	108,130				108,130
Biological carcinogenesis...........	105,046				105,046
Nutrition.................	23,988		2,420	2,555	28,963
Tumor biology.............				154,406	154,406
Immunology................	473	1,069		89,160	90,702
Diagnostic research.......		62,592			62,592
Preclinical treatment research.......			176,801		176,801
Clinical treatment research.......			180,634		180,634
Rehabilitation research.................			3,997		3,997
Total, research...........	$288,319	$77,643	$365,333	$246,121	$977,416

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Crosswalk - Research Programs
(dollars in thousands)

Fiscal Year 1987
Estimate

	Cause & Prevention Research	Detection & Diagnosis Research	Treatment Research	Cancer Biology	Total
Research Programs					
Epidemiology.............	$50,270	$13,708	$1,481		$65,459
Carcinogenesis (physical & chemical)....	108,309				108,309
Biological carcinogenesis...........	103,720				103,720
Nutrition.................	23,000		2,482	2,541	28,023
Tumor biology.............				151,089	151,089
Immunology................	434	988		88,227	89,649
Diagnostic research.......		63,476			63,476
Preclinical treatment research.......			176,545		176,545
Clinical treatment research.......			180,807		180,807
Rehabilitation research.................			3,813		3,813
Total, research...........	$285,733	$78,172	$365,128	$241,857	$970,890

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Research Programs Summary
(dollars in thousands)

	1985 Comp. Actuals	1986 Revised Estimate	1987	Increase or Decrease
Research Programs				
Epidemiology.............	$69,460	$66,145	$65,459	-$686
Carcinogenesis (physical & chemical)....	106,273	108,130	108,309	179
Biological carcinogenesis..........	102,845	105,046	103,720	-1,326
Nutrition................	28,689	28,963	28,023	-940
Tumor biology............	151,102	154,406	151,089	-3,317
Immunology...............	93,112	90,702	89,649	-1,053
Diagnostic research.......	60,544	62,592	63,476	884
Preclinical treatment research.......	165,890	176,801	176,545	-256
Clinical treatment research.......	180,401	180,634	180,807	173
Rehabilitation research................	2,127	3,997	3,813	-184
Total, research..........	960,443	977,416	970,890	-6,526
Resource Development......	136,724	129,846	123,888	-5,958
Cancer Prev. & Control....	66,569	63,213	63,311	98
Total....................	$1,163,736	$1,170,475	$1,158,089	-$12,386

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NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Obligations by Object

	1985 Comparable Actuals	1986 Revised Estimate	1987 Estimate
Total number of full-time permanent positions..................	1,971	1,971	1,971
Total compensable workyears:			
Full-time equivalent employment.......	2,326	2,169	2.174
Full-time equivalent of overtime and holiday hours...........	23	25	25
Average ES salary.....................	$66,232	$66,232	$66,232
Average GS grade......................	9.14	9.14	9.14
Average GS salary.....................	$28,224	$28,224	$28,224
Average salary, grades established by act of July 1, 1944 (42 USC 207)..	$35,361	$35,361	$35,361
Average salary ungraded positions.....	$23,206	$23,206	$23,206
Personnel compensation:			
Full-time permanent..................	$54,453,000	$54,658,000	$55,331,000
Other than full-time permanent.......	20,040,000	20,272,000	20,272,000
Other personnel compensation.........	2,681,000	2,719,000	2,719,000
Special personal services payments...	4,595,000	4,629,000	4,629,000
Total personnel compensation....	81,769,000	82,278,000	82,951,000
Personnel benefits...................	11,285,000	11,300,000	11,405,000
Benefits to former personnel..........	-4,000	0	0
Travel and transportation of persons..	4,017,000	4,389,000	4,665,000
Transportation of things..............	730,000	730,000	730,000
Communications, utilities, and rent...	6,823,000	6,959,000	7,098,000
Printing and reproduction....	4,907,000	6,036,000	6,502,000
Other services			
Project contracts....................	161,622,000	154,278,000	150,592,000
Centrally furnished services.........	54,429,000	68,612,000	68,441,000
Standard Level User Charge...........	1,922,000	2,210,000	2,381,000
Other................................	64,789,000	32,244,000	35,687,000
Supplies and materials................	26,057,000	26,578,000	27,110,000
Equipment.............................	8,365,000	8,532,000	8,703,000
Land & structures.....................	4,000	0	0
Grants, subsidies, and contributions..	737,013,000	766,324,000	751,819,000
Insurance claims and indemnities......	5,000	5,000	5,000
Interest..............................	3,000	0	0
Total obligations................	$1,163,736,000	$1,170,475,000	$1,158,089,000

National Cancer Institute

Significant Items in 1981 Senate Appropriations Committee Report

Item	Action Taken or To Be Taken
"As in the past, the Committee continues its commitment to support for basic research in cancer and believes that other areas are critical to the effort to conquer cancer. Cancer centers and clinical cooperative groups, for example, are vital national resources and must continue to receive adequate support. In its fiscal year 1980 report, the Committee noted its concern that cancer center core grants had been treated differently from other grants and have been budgeted on the average of 17 percent below peer-reviewed levels, and recommended its desire that these core grants be funded at full peer-reviewed levels. The Committee has learned that this instruction was interpreted to mean that only new and competing grants should be funded at peer-reviewed levels. These were funded at 90 percent of such levels, but then noncompeting continuation awards were funded at the 83 percent level, as they had previously. The Committee desires that all such core grants, competing and noncompeting, should, within budgetary constraints, be funded at the peer-reviewed levels that had been assigned."	Within the constraints of the current budget, the National Cancer Institute is making every effort to comply as closely as possible with the recommendations of peer reviewers with respect to funding of cancer centers.
"Similarly, the clinical cooperative program, which has contributed so much to the treatment advances we have, has not been funded at recommended levels for several years. It is through the clinical cooperative groups that the NCI performs most of its clinical research, with emphasis on protocol-based research into treatment and prevention. The groups, in fact, have actually been receiving lower budgets in comparison from prior-year levels.	Within the constraints of the current budget, the National Cancer Institute is making every effort to comply as closely as possible with the recommendations of peer reviewers with respect to funding of clinical cooperative research.
The Committee encourages NCI, to the extent possible, to fund both these programs at levels that are consistent with peer reviewers' recommendations."	

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1986 Amount Authorized	1986 Revised Estimate	1987 Amount Authorized	1987 Budget Request
Research and Investigation........	Section 301	42§241	Indefinite		Indefinite	
National Cancer Institute.........	Title IV, Part A	42§284c	$1,262,000,000	$1,135,339,000	$1,344,000,000	$1,129,479,000
	(Sec. 408 (a)(1)(A))		(1,194,000,000)		(1,270,000,000)	
	(Sec. 408 (a)(1)(B))		(68,000,000)		(74,000,000)	
National Research Service Awards..	Section 487	42§288	$244,000,000 1/	$29,512,000	$260,000,000	$28,610,000
Total Budget Authority..........				$1,164,851,000		$1,158,089,000

1/ This training authority is shared with other research training programs of the National Institutes of Health, Alcohol, Drug Abuse, and Mental Health Administration, and the Health Resources and Services Administration.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1977	687,670,000	773,412,000	850,000,000	815,000,000
1978	824,772,000	837,188,000	925,252,000	872,388,000
1979	878,410,000	888,800,000	937,108,000	936,737,000
1980	938,506,000	961,158,000	1,000,000,000	999,869,000
1981	982,901,000	993,600,000	988,284,000	989,355,000
1982	902,832,000 2/	1,030,356,000	1,034,180,000	986,617,000
1983	955,449,000	981,441,000	985,711,000	987,618,000
1984	986,681,000	1,044,868,000 3/	1,062,017,000 3/	1,093,018,000
1985	1,101,069,000	1,084,950,000 4/	1,187,693,000	1,196,528,000
1985 Proposed Rescission	-4,362,000			
1986	1,126,012,000	1,221,590,000 5/	1,271,555,000	1,258,159,000
1986 Sequester	-53,868,000			
1986 Proposed Rescission	-6,800,000			
1987	1,158,089,000			

1/ Reflects enacted supplementals, rescissions and reappropriations.

2/ Reflects the September Amendment; the original request was $1,025,941,000.

3/ Excludes $23,861,000 in NRSA training programs not considered.

4/ Excludes $89,153,000 for NRSA, cancer control and construction activities not considered.

5/ Excludes $37,358,000 for Construction activities and NRSA training programs not considered.

National Cancer Institute

Justification

	1986 Appropriation	1986 Available After Sequestering	1986 Revised	1987 Estimate
Research	$1,029,308,000	$ 984,216,000	$ 977,416,000	$ 970,890,000
Resource Development	135,627,000	129,846,000	129,846,000	123,888,000
Cancer Control	66,075,000	63,213,000	63,213,000	63,311,000
Total	$1,231,010,000	$1,177,275,000	$1,170,475,000	$1,158,089,000

General Statement

OVERVIEW

The National Cancer Program's investment in basic research has led us today to an unprecedented understanding of the cancer cell. This knowledge of the cancer process has major implications for cancer prevention, diagnosis, and treatment. As the ongoing basic research--now at its most productive period in history--develops a comprehensive understanding of the step-wise cancer process, that new knowledge is put to work in practical ways that benefit people.

Based on this new knowledge of cancer biology, the NCI has major research efforts under way: to prevent cancer; to reverse the cancer process by nudging a transformed cell back to normal; to selectively destroy cancer cells; to boost the immune system, our natural defense against cancer; and to block the ability of cancer cells to spread and kill--a process called metastasis.

Researchers have tapped into the genetic machinery at the heart of the cell and found minute, but critical, differences in genes of normal and cancer cells. They have discovered oncogenes--genes associated with cells becoming cancerous. Cancer cells are renegades but, although they exert their lethal effects by growing out of control, they appear to be immature and somewhat confused cells, using in aberrant ways the genetic mechanisms established for normal growth and development.

Cancer researchers have long thought that cancer is a multistage process with intricate circuits and switches, working at different points of disease progression and at different times. Now basic research is unraveling that process and presenting new opportunities for the control of cancer. Most recently, scientists have been studying the chemical switches which trip--one after another--a cascade of events that control oncogenes. They have learned that cancer is over 100 different diseases, but that all may share a basic mechanism that sets off the disease. As a result, all cancers are becoming increasingly vulnerable as researchers probe further into the cancer process.

The multistage cancer process means that only after a sequential and prolonged series of steps can normal cells turn into cancer. Generally, scientists divide the process of carcinogenesis into initiation and promotion stages. Tumor development begins with exposure to an initiator, followed by multiple exposures to one or more promoters. Regardless of whether the inducing influence is a chemical or biological agent, the existence of many stages allows multiple strategies for prevention. For example, scientists have identified and isolated more than 30 oncogenes involved in transforming normal, healthy cells to cancer. These oncogenes appear to play roles at every step of the pathway to cancer, from initiation through promotion. Initiators or promoters can "turn on" or activate an oncogene, causing, in turn, increased production of a protein that in some way regulates or controls cell behavior or misbehavior.

Initiation of the cancer process begins, for example, when chemical damage to DNA (the genetic material of a cell) activates an oncogene or inactivates a regulatory gene. In addition to chemicals, other initiators include agents such as viruses and radiation. Tumor promoters, which may include such agents as fat in the diet, hormones, or certain compounds found in cigarette smoke, do not cause cancer by themselves, but they facilitate the cancer process, pushing a cell closer and closer to cancer. They are only able to do this after a cell has been initiated. While it has been known for some time that cancer involves two basic stages, recently, research emphasis has focused on how promoters work, and on how to reverse the later stages. This is important because it is assumed that most individuals have been exposed to "initiators", so that a quick way to lower cancer incidence is through antipromoters.

Such an approach promises to yield rapid results in the prevention of cancer in large numbers of people. This can be accomplished by removal of an agent (such as estrogen or cigarette smoke, or perhaps lowering fat in the diet); or by use of antipromoting agents (such as vitamin A derivatives or micronutrients in the diet) to block tumor growth factors or oncogenes.

An individual's risk of cancer is determined by a complex and interacting set of variables. In view of the increasing knowledge of the importance of lifestyle factors such as diet, tobacco, and alcohol in the cause and prevention of cancer, particular emphasis is being placed in our Cancer Prevention and Control Program, discussed later, in a major thrust to test ways to block the later promotion stages of the cancer development process.

Powerful evidence already exists that this approach works. For example, curtailing wide use in the 1970's of the "promoter" estrogen, used for menopausal symptoms, led to a dramatic, fast reduction in uterine cancer. Cigarette smoke contains both initiators and promoters. This year, NCI reported from the SEER (Surveillance, Epidemiology and End Results) Program that the incidence of lung cancer in white men has decreased significantly for the first time in at least 50 years (from 82.7 new cases per 100,000 white men in 1982 to 79.3 in 1983). This provides evidence that the exposure to chemical promoters does not irreversibly destine a person to develop cancer and that people can successfully reduce their cancer risk by quitting smoking or not taking up smoking. The interval from smoking cessation to a return to normal risk of cancer is under a decade for some smoking-related cancers in man.

As researchers continue to trace the intricate markings of cancer, we are confident that the mechanisms that lead a cell to become malignant will become clear. The step from the point to more effective prevention, diagnosis and treatment of cancer may well be a relatively short one in medical history.

PROGRAM ACCOMPLISHMENTS

BASIC BIOLOGY

The investment in basic biology has resulted in the development of major new technology that allows scientists to put knowledge to work. The discovery of the role of two kinds to enzymes in the 1970s has been especially important. "Restriction enzymes" were found in bacteria and "reverse transcriptase" in cancer viruses. Restriction enzymes are nature's scissors for cutting up strips of DNA--the molecules which contain the genes. Reverse transcriptase is the chemical catalyst for copying the genetic material of a virus (RNA) into the genetic material (DNA) of a cell. This finding opened up the door for copying and incorporating foreign genetic material into the DNA of a cell. The discovery of restriction enzymes and reverse transcriptase helped lead to the development of many techniques enabling scientists to cut and splice genes (known as recombinant DNA). With these tools in hand, researchers are able to sequence and scrutinize pieces of DNA and decode nature's messages. It has become routine to read genetic messages at the molecular level.

Researchers have been unraveling the multistep cancer process and now have discovered more than 30 oncogenes that are related to transformation of cells to cancer. Knowledge of cancer biology today has brought together various pieces of the cancer puzzle. Once seemingly diverse research concepts from virology, chemical carcinogenesis, biology, and genetics have come together with startling unity.

Counterparts to oncogenes, called proto-oncogenes, are involved in our normal development from embryo to adult. In normal development, some cells must also travel along precisely programmed pathways from one site to other sites where they specialize or "differentiate"--acquiring the capacity to carry out the tasks of one organ, such as the liver, lung, or heart. In the cancer process, this migratory capacity appears to be reactivated when cancer cells travel from the primary cancer through the bloodstream or lymphatic system and develop secondary deposits in the body called metastases.

An oncogene may be activated by mutation, a chemical, a virus, or radiation, or by moving to a new location on a chromosome where it is placed next to inappropriate switches that signal it to "turn on" or "off". For example, scientists have already found evidence of the activated *ras* oncogene (which has a mutation) in a number of human cancers, including lung, colon, and bladder cancers.

Five different oncogenes associated with blood system tumors have been identified with specific translocations on chromosomes. In a type of chronic myelogenous leukemia, which has a special marker chromosome, the *abl* gene appears at the same translocation in 100 percent of tumors. In Burkitt's lymphoma, when the *myc* gene is translocated, it falls under "promoters" or control elements that usually regulate production of antibodies. Because the gene has been moved, it can be turned on at a high level by new "switches" or controls. When such events occur, the protein products of the gene can be excessively or incorrectly produced, leading to uncontrolled growth of the cell which is cancer.

Much research has been aimed at identifying human oncogenes, their molecular mechanisms of action, and how their protein products function in cancer. Close ties have been found between some oncogenes and substances which stimulate the growth of cells (growth factors). Oncogenes also have been implicated as important influences on the aggressiveness of cancer cells and whether they spread and invade distant, vital organs--in medical terms, how they metastasize. Recently, researchers have found that activation of more than one oncogene or the presence of many copies of it (called gene amplification) is closely associated with the metastasic process. For example, a breast cancer cell line, containing an oncogene, escaped normal, hormonal regulation and became more aggressive with the addition of a second oncogene.

A new development, important for streamlining studies of oncogenes, is a technique called "marching down the chromosome." Scientists isolate the ends of large DNA fragments and use them to probe and isolate additional ends of DNA further along the chromosome. With this new method, much information is obtained quickly so that new genes can be identified, compared and sequenced.

A few years ago, research focused on the discovery of oncogenes. The field has now moved toward also understanding the products that oncogenes make and the "control switches" that turn these genes on and off. These switches can be either next to an oncogene--called flanking sequences of DNA--or be removed some distance from it. This research provides vital new information for preventing cancer--for turning its switches "off." Along these lines:

- This year, the protein products of the *erb*-B and *fms* oncogenes were found to be defective receptors for cell growth factors, no longer interacting appropriately with growth factors. These data add to an increasing body of evidence that associates oncogenes closely with cell growth factors and their receptors. Understanding what controls the regulation of oncogenes can be used to prevent their activation as well as to develop methods to improve on specific diagnostic and treatment approaches. For example, oncogene products could provide targets for monoclonal antibodies, designed to "home in" on specific markers on cancer cells. There are multiple steps from initiation to a final cancer, and such antibodies to growth factors or their receptors could block a critical step.

- The "flanking" DNA sequences--control switches which often border genes--bind specific proteins that control gene expression. Major breakthroughs in use of recombinant DNA technology to clone flanking sequences, and the development of methods for isolating these critical regulatory proteins, offer new opportunities for studying and understanding the control of gene expression at the most refined levels. Because cancer is a disease of genes being expressed abnormally--in the wrong place at the wrong time--it is crucial to study such factors that control gene expression in normal and cancer cells.

- It is now possible to make combinations of different oncogenes and their flanking DNA sequences in the laboratory, then inject these "foreign" genes into fertilized mouse eggs, and to produce mice in which every cell contains the foreign genes ("transgenic" mice). Much of cancer research in the past has focused on the use of cell lines in laboratory test tubes. The use of "transgenic" mice offers an invaluable tool to study oncogenes, drug resistance genes, and cancer promoters in living animals.

CAUSE AND PREVENTION

An individual's risk of cancer is determined by a complex and interacting set of variables that includes genetic makeup, lifestyle, and environmental and occupational influences. Results from basic, chemical, and epidemiologic research continue to indicate that cancer is a multistep process. With recently developed techniques for tissue culture, it is now possible to examine the progression of the cancer process in minute detail. For example, scientists are now able to grow in the laboratory a wide variety of human tissues. Many of these tissues can be maintained in chemically defined culture media that do not require blood serum or plasma. This enables scientists, under controlled conditions, to study at the cellular and molecular level the many phenomena believed necessary for cancer formation and to test compounds for their ability to prevent or block cancer.

Previously, researchers have studied the phenomena of cancer initiation and promotion chiefly in animal models of skin cancer development. This past year, scientists have shown that a well-known promoter of skin tumors in animals, called TPA or 12-O-tetradecanoyl phorbol-13-acetate, binds avidly to a member of a group of enzymes called protein kinases. Specifically, an enzyme called protein kinase C, which is critical for regulating normal cell growth and development, is the cellular receptor for TPA. The binding of TPA to this receptor seems to be essential for tumor promotion by TPA and other related chemicals. It is of interest that a number of oncogene products are also protein kinases. Studies on this enzyme and attempts to modulate this receptor will be expanded in the coming year.

Two different oncogenes have been identified in chemically induced cancers of rats: oncogenes of the ras family were found in kidney cancers; and cancers of the peripheral nervous system contained an oncogene of the erb-B family. These findings indicate that specific oncogenes may be expressed in specific types of cancers caused by chemical carcinogens.

Studies on transforming growth factors (TGF) are being expanded to evaluate their role in cancer. A peptide growth factor, TGF-beta, has now been purified, cloned, and its complete amino acid sequence determined. In concert with another growth factor, this peptide can change normal cells into cancer cells. However, under other conditions, TGF-beta can also inhibit the growth of cancer cells. This growth factor is of interest because it plays an intrinsic role in inflammation and tissue repair, and can stimulate the formation of connective tissue and collagen in animals. In animal experiments, TGF stimulated the formation of new blood vessels, a phenomenon known to occur during the growth of a solid tumor.

Another form of more distal control of genes is found in "switching" genes of several families of tumor viruses. These genes code for "trans-acting" proteins which appear to play a role in the reproduction of viruses. Recently, members of human T-cell lymphotropic virus (HTLV) family, which now include the human cancer virus HTLV-I, a human RNA virus called HTLV-II that is not yet linked consistently to a specific disease, and HTLV-III (the AIDS virus) all contain genes for powerful transactivating proteins. In addition, an RNA cancer virus of cows also appears to produce a "trans-acting" factor that stimulates the viruses' own reproduction. In the coming year, more research will go into identifying such proteins, to determine how they act to increase virus production and, often, cancerous cell growth in the cells they infect.

Previously, cervical cancer was tenuously associated with infection by herpes viruses. Now research indicates that approximately 80 percent of all premalignant and malignant cervical tumors contain human papillomavirus (HPV) DNA. Over 40 types of HPV exist, only a few of which are associated with cervical cancer. In recent work, NCI-supported scientists have found genes from the same strains of papillomavirus in both the primary tumors and metastases of several cervical cancer patients, while tissues from women free of cervical cancer did not contain these genes. The findings lend further support to the hypothesis that these specific strains of papillomaviruses may be responsible for these patients' genital cancers.

The list of cancers associated with tobacco products continues to grow. In particular, recently completed studies indicate that kidney cancer is another one of the cancers (besides lung cancer) strongly associated with smoking. In addition, the use of smokeless tobacco has been linked to high rates of oral cancer, particularly among women in the southern United States. In the coming year, research will intensify to clarify possible risks associated with the use of snuff and chewing tobacco because of their increased use among youth. The NCI co-sponsored, in early 1986, a consensus development conference that pointed up the adverse health implications of smokeless tobacco use. In addition, the Institute is sponsoring several studies that will help quantify risks of passive smoking--the risks of nonsmokers who are exposed to the smoke of others.

Basic cancer research continues to have major spin-offs for new knowledge in other diseases as well. Scientists have found a new genetic marker for cystic fibrosis (CF), an oncogene located close to the gene responsible for the disease, on human chromosome number 7. Although the marker is diagnostic for patients with cystic fibrosis, for carriers within families with a history of the disease, or the general population (1 in 20 are carriers), isolation of the CF gene itself is required, a task now technically feasible because of the new findings.

Researchers have found that the cerebrospinal fluid cells of some multiple sclerosis (MS) patients contain genetic information from a virus related to the HTLV family. Although the virus has not yet been isolated, the findings suggest that the patients are infected with a new virus from a family of viruses some of which are known to be able to infect cells of the central nervous system.

CANCER PREVENTION AND CONTROL

Cancer's prevention and control requires efforts in several directions: reducing or eliminating exposure to agents that initiate or promote cancer; interfering in the cancer-causing process; increasing the percentage of people

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who follow cancer detection practices; and increasing the number of patients who receive state-of-the-art treatment.

Capitalizing on information from basic research that cancer is a multistage process, NCI is now investigating practical ways to prevent cancer by interfering with the late, "promotion" stages of the process, perhaps even by blocking the activity of oncogenes. An extensive research program on diet and cancer, for example, is probing the role of specific foods and food groups to find ways of preventing cancer through dietary modifications. Some nutritional factors, such as fat, are thought to promote cancer, while others, such as fiber, are thought to inhibit some cancers. As much as 35 percent of cancer deaths may be related to diet.

A major feasibility study is under way to determine whether low-fat diets can reduce breast cancer incidence in women who are at high risk because of a strong family history of the disease. In the trial, the dietary fat levels will be about 20 percent or less of total caloric intake, about half the level consumed by most Americans.

Another study is looking at the association of diet and breast cancer in young Oriental women. When Orientals migrate to the United States, their low breast cancer rates rise over a generation or two toward American rates which are higher. The study participants and many of their mothers will be interviewed about their dietary habits during childhood and adolescence to determine the influence of foods on breast cancer.

There is much evidence showing that increased fiber consumption can reduce the risk of some cancers, and the Institute is sponsoring several studies to find out how fiber works to reduce risk. One recent study points to the inhibitory role of phytic acid, which is present in many diets rich in grain fibers. Another study indicates the uronic acid in vegetable fiber also has an inhibitory effect. Once fiber's role is better understood, it may be possible to issue more specific dietary guidelines for the public. Guidelines now simply recommend doubling dietary fiber in the normal American diet.

Meantime, a number of studies are under way to look at the chemistry and function of various types of fiber. One of the studies examines the effect of fiber on colon function, particularly the impact of various fiber types on fatty acids, bile steroids, bacteria, mutagens and fecal bulk in human volunteers. Another study attempts to find better methods of determining the fiber content of foods commonly eaten in the United States.

In addition to dietary modification, the NCI is exploring chemoprevention as a way of interfering with the promotion stages of the cancer-causing process. Chemoprevention introduces selected micronutrients and other substances into the diet to reduce cancer incidence. Already 450 agents have been identified in the literature as having activity that may inhibit cancer; indepth analysis has begun on about 15 percent of them. The 26 human chemoprevention studies now underway test pure chemicals or micronutrients in precise doses to determine preventive effects. Among the agents under study are vitamins A, C, and E, beta-carotene, and certain trace elements such as selenium and zinc. If even one of these studies should prove successful, a substantial number of cancers would be preventable.

Investigators in two studies are providing multiple vitamin-mineral supplements, including beta-carotene and a balanced multivitamin pill, to people in China with nutritional deficiencies who are at high risk of esophageal cancer. The aim is to see if such supplements can reduce the mortality rate from this disease.

In another study, researchers, in collaboration with colleagues in Finland, are trying to determine if daily oral supplements of beta-carotene and vitamin E can help prevent lung cancer among men who smoke cigarettes.

Cancers caused by tobacco use are amenable to intervention. In fact, some elements of cigarette smoke itself apparently serve as cancer promoters in the second stage of carcinogenesis. This concept is bolstered by the fact that smokers who quit, particularly those who smoked less than 20 years, can reduce their risk of lung cancer to about that of the general population after about 10 years of nonsmoking.

Because 30 percent of all cancer deaths are directly attributable to smoking, NCI is engaged in a concerted research effort to find effective ways to get smokers to quit, and to prevent nonsmokers from beginning the habit. For example, NCI is funding 34 tobacco-related intervention studies--involving more than 5 million people--to find ways of reducing smoking in large populations of Americans. Among those targeted are adolescents, minorities, women, and smokeless tobacco users.

Another project about to get under way will study approaches to a nationwide community-based smoking cessation program for heavy smokers--the group at highest risk of cancer. Successful approaches found by all of these studies, scheduled for completion during the 1980's, will be applied in large target population demonstration programs to have marked public health impact.

SEER (Surveillance, Epidemiology, and End Results Program)

Meantime, NCI continues to track the incidence, survival and mortality rates of cancer in the United States. SEER, begun in 1973, has now been in operation for a sufficient time to allow consistent estimates of cancer patient survival changes. The potential of the program is just beginning to be realized as the data collected over the past decade have begun to mature. In many ways SEER acts as our compass. Studies of differences in incidence and survival among populations are valuable in directing the NCI Cancer Control Program and providing new research leads in such areas as avoidable cancer mortality and differences in treatment delivery.

Annually, NCI updates survival statistics for cancer patients. The steady progress now being made in cancer treatment is beginning to have an impact on a number of cancers and on national cancer survival statistics. Five-year relative survival is often used as a general indicator of prognosis and the potential for cure. Five-year relative survival rates have reached 50 percent for patients with serious cancers. But even with steadily encouraging survival rates, the statistics do not yet reflect the pace of progress today for several reasons.

First, there is a built-in time-lag. The impact on statistics of treatment advances entering the clinic in 1976 were measured in 1981, the latest year of available SEER data. Thus, statistics at hand reflect results of far earlier treatments--and do not reflect more recent advances.

Another reason that cancer survival statistics have not improved at a faster rate is that new, effective therapy has not always moved swiftly from the clinical trials setting to routine and accurate application in medical practice. It has been estimated that if every patient with cancer in the U.S. were to receive the best treatment available today, there would be a 10 percent improvement in 5-year survival rates--a savings of 40,000 lives per year.

The NCI has initiated a number of programs to speed the transfer of new advances from basic and clinical research into the community at large. These efforts include the network of cancer centers and cooperative groups of clinical researchers, which are established around the country; the Community Clinical Oncology Program (CCOP), which connects practicing physicians with research programs at the cancer centers and the cooperative groups; and Physicians' Data Query (PDQ), which is a computerized information system that allows physicians nationwide to easily and quickly access the most up-to-date information about cancer treatment and clinical trials.

NCI encourages both physicians and patients to be concerned that state-of-the-art treatment is practiced and that adequate drug dose is given in each case. PDQ serves as a convenient checkpoint for physicians. Patients can ask their physicians to use PDQ or can request it from the Cancer Information Service (toll-free 1-800-4-CANCER) to share with their physicians. To implement the most effective treatments represents a major challenge to the NCI and the medical profession. Further improvements in cancer patient survival rates hinge on proper delivery of care.

Cancer Among Minorities

Future gains against cancer will depend to an important degree on solving the problem of excess cancers and cancer deaths among minority populations. As a result of this problem, pointed up dramatically in recent years by NCI's SEER program, the NCI is sponsoring a special initiative to address cancer problems in minorities, with early emphasis on black Americans.

Programs to address the significant cancer rate differences between blacks and the general population include:

- A major campaign initiated in 1985 to let black populations know what each individual can do to reduce personal risk of cancer.

- A Black Research Network, initiated early in 1986 to address the research issues of cancer prevention and control in black populations. This network includes all of the major black-oriented medical schools in the United States.

- Three solicitations asking non-Federal investigators to submit proposals for projects designed to reduce cancer rates in black populations.

- A Comprehensive Minority Biomedical Program (CMBP) to involve minorities significantly in cancer-related research activities. The program emphasizes increased funding for research by minority scientists; concerted enrollment of minority physicians and patients in cancer treatment studies nationally; and training and manpower development. For example, the CMBP contributes to the support of NCI's clinical cooperative groups to enable NCI's research to reach and support those minority populations which are particularly susceptible to certain types of cancers. These supplemental awards provide data management and other expenses to allow participation of minority institutions as satellite affiliates, thus expanding the clinical trials research network to access a greater number of patients from minority populations.

Applying Research Findings

The National Cancer Institute, coordinating with the Centers for Disease Control, has begun to work intensively with state and local health departments. Those agencies' resources and access to high-priority target populations are needed to mount effective control measures against specific cancer problems in local communities.

The NCI, which already has initiated discussions with 36 states, will help those agencies identify and address the most important cancer problems facing their regions. NCI support will range from technical assistance to develop the capacity for conducting cancer control programs, to tracking progress.

With this kind of support, a state or local agency could identify a county where the mortality rate from cervical cancer, for example, is higher than the national average, determine the cause of the problem, and then work to cut the death rate through control measures, such as county-wide Pap testing and followup for populations with low access to screening services.

In 1986 and 1987, NCI will ask agencies to submit proposals for the support they need to plan and mount effective anti-cancer programs. The support will help the agencies identify problems, analyze research data, build coalitions, and plan and evaluate programs.

DIAGNOSIS AND TREATMENT

Understanding the multistep cancer process is beginning to have an impact in the clinic as basic knowledge of cancer biology and new technology move rapidly to the cancer patient's bedside. Molecular biology and genetics are being applied to study cells of cancer patients to define gene rearrangements, amplification, translocations, and cell membrane changes. Techniques employing monoclonal antibodies are being used for diagnosis and treatment. The time-lag between research discovery and application is being shortened by partnerships between the laboratory and clinic.

Diagnosis

Recombinant DNA techniques and monoclonal antibody technologies that have contributed so much to unfolding the cancer story, now hold enormous promise for rapidly diagnosing and characterizing tumors and for treating patients. Breakthroughs in basic tumor biology have shown that cancer development involves genetic alterations. Gene technologies are promising not only for identifying specific types of tumors but for identifying populations at high risk for cancer. Identifying such populations will result in more targeted prevention programs and effective screening programs for early detection and prompt treatment.

Gene technology has been increasingly applied to cancer diagnosis. Specific DNA "probes" are now used to identify genetic alterations in tumor tissue. The presence of oncogenes can be detected and the amount of their gene products measured. Recently, differences in the levels of the product of the ras oncogene, $P21^{ras}$, have been correlated with various stages of colon cancer. An important goal is to characterize such oncogene products and also to develop new therapies to inhibit their production or action, thereby increasing a patient's survival.

Characterizing gene amplification in different tumors is an important new advance in cancer diagnosis. Recently, amplification of the N-myc oncogene has been linked to increased aggressiveness of neuroblastomas, and amplification of either the c-myc or the c-myb oncogene has been associated with different subsets of acute myelogenous leukemias. Researchers have also discovered that small cell lung cancer patients whose cells contain amplified c-myc and N-myc oncogenes have more aggressive disease and shortened survival. Thus, it is now possible to predict the clinical aggressiveness of neuroblastoma, small cell lung cancer, and acute myelogenous leukemia, because of recent studies characterizing oncogenes. Knowing how far advanced cancer cells are in the multistep progression of disease is important for choosing the best way to intervene.

While monoclonal antibodies continue to be a major tool for basic research in studies of cell biology and immunology, they are increasingly being used to identify new tumor markers for diagnosis and for more accurate classification of tumors, and present new possibilities for treatment.

Monoclonal antibodies have been applied directly to biopsy samples to aid in tumor characterization and have also been used to detect metastatic breast cancer cells in the body fluids of some patients. These antibodies, which can be tagged with radioactive tracers, have also shown promise in clinical studies to detect extent of disease (including hidden metastases) in patients with colon cancer and melanoma. Monoclonals have already been useful in distinguishing one type of lymphoma from another. It is important to diagnose cancer early and accurarely in order to choose the best treatment.

Specific monoclonals have also been developed to detect cytoskeletal proteins--proteins that form the skeleton or scaffolding of the cell. They are now being widely used to identify the cell of origin of tumors and especially to distinguish sarcomas from carcinomas.

Many advances in nuclear medicine and diagnostic imaging are also dependent on monoclonal antibody technology. Research efforts are under way to develop monoclonal antibodies of human origin for use here. They would not provoke a harmful immune reaction like monoclonals of animal origin in patients who have repeated administration, and are expected to improve the sensitivity of tests.

This year, there have been major advances in imaging technology. Investigators have now used sodium and phosphorous imaging techniques in Magnetic Resonance Imaging (MRI) to distinguish cancer from benign tumors. MRI is proving useful for defining the extent of tumor involvement of lung, liver, brain, and other organs.

Treatment

Progress continues in surgery, radiotherapy, and chemotherapy as effective treatments for many cancer patients. This year, for example, lumpectomy followed by radiation for early-stage breast cancer was reported to be as effective as mastectomy; progress continued in arming monocolonal antibodies with radioisotopes; and adjuvant chemotherapy (use of anticancer drugs to prevent cancer recurrence by eradicating microscopic spread of tumor cells) gained new recognition. Positive adjuvant treatment studies in breast cancer, rectal cancer, colon cancer, and adenocarcinoma of the lung were reported during 1985. Such adjuvant treatment of cancers widely applied could be expected to save the lives of 22,000 Americans each year.

Already, the steady increase in survival rates for cancer patients suggests that cancer treatment is having its impact. In 1963, the 5-year relative survival rate for cancer patients was 38 percent. Today, 50 percent of people with serious cancers are curable. Data from our Surveillance, Epidemiology, and End Results (SEER) Program continue to show that significant gains in survival have occurred and have been maintained for many cancer sites including Hodgkin's disease, the major cancers of children, and testicular cancer. This year, a worldwide review of breast cancer clinical trials indicated that appropriate use of chemotherapy in patients of high risk for recurrence could reduce early mortality from this disease by 25 percent in women under 50 years of age, and, nationally, we are beginning to see a decrease in breast cancer mortality rates in this age group.

A major obstacle to curing cancer with drugs has been the resistance that certain cancer cells develop to the drugs. Recently, a new cell surface marker, related to this phenomenon, was discovered and found to be the product of gene amplification. The marker, the P170 glycoprotein, offers a target for monoclonal antibody. New studies indicate that an antibody to P170 may reverse the cancer cell's resistance to existing anticancer drugs. Other research findings this year suggest that the basic process of cell transformation to cancer may at the same time amplify a cell's defenses against toxic substances so that it strongly resists foreign agents such as anticancer drugs. Increased levels of certain enzymes--protein kinase C and glutathione transferase--involved in natural defenses against toxins, have recently been found in high levels in drug resistant cells. The increased levels mimic those seen in the early stages of cancer transformation and offer, for the first time, a link between drug resistance and the fundamental cancer transformation process. This research also suggests new targets for cancer drug design, such as inhibitors of protein kinase C.

The past year has also witnessed major advances in the development of entirely new approaches to cancer treatment. These approaches are based on the knowledge and tools of modern molecular biology, immunology, and genetics that have provided new targets for cancer therapy.

Cancer biologists have been mapping the step-wise processes by which cancer cells escape immune system destruction, fail to differentiate (mature as normal cells), metastasize and invade vital organs, as well as the ways cancer cells develop resistance to anticancer drugs, stymying efforts for effective treatments. Now researchers also are identifying growth factors that control tumor proliferation and signal oncogenes to express their products. Progress in each of these research areas has led to new cancer treatments.

Why and how the immune system in cancer patients does not recognize tumor cells as foreign to the body is one major research area. The surface of the tumor cell is the part of the cell that is exposed to attack by the immune system and may be affected by the expression of oncogene products. Oncogene products may provide recognition sites for monoclonal antibodies which can deliver drugs, toxins, biologicals, or radionuclides that kill tumor cells.

Meantime, a fourth modality of treatment, the use of biologicals (substances that are naturally found in the body), is joining chemotherapy as a systemic treatment. Surgery and radiotherapy can control localized tumor, but once a cancer has begun to spread, then a systemic or "body-wide" treatment is needed.

This year, a very promising trial of biologicals was reported, using what is called adoptive immunotherapy. This form of treatment employs the transfer of anticancer immune cells directly to the cancer patient. Scientists at NCI exposed the patients' own white blood cells in culture to high concentrations of T-cell growth factor, (IL-2), discovered earlier by a researcher at NCI. This technique generated Lymphokine-Activated Killer (LAK) cells which were then transfused back into the patient along with doses of systemic IL-2. Early results in patients with advanced cancer have been most promising. NCI is expediting national trials to test this new treatment across the country. The clinical network of cancer centers and cooperative groups of researchers is in place and readily mobilized. The effects of LAK are also being studied in combination with surgery or chemotherapy.

Using recombinant DNA technology, the genes of several body proteins, interferon, IL-2, and, most recently, tumor necrosis factor (TNF), have been cloned, permitting preparation of these important substances on a scale large enough to conduct clinical studies. These factors are all being tested now for their antitumor effects in cancer patients. Excellent responses to interferon have been seen in hairy-cell leukemia, tumors of the lymph nodes, and kidney cancer. In laboratory studies, human TNF, a protein isolated from human white blood cells, has been highly toxic to cancer cells and appears to have little effect on normal tissues. It has also been effective in treating experimental animals with cancer.

An important property of the cancer cell that has become a target for treatment is its failure to differentiate or mature. Studies are under way of agents that can make the cell become more mature or noncancerous. The retinoids, analogs of vitamin A, have produced clinical responses in patients with pre-leukemias, acute promyelocytic leukemia, and early cancers of the mouth, skin and cervix.

An area of high priority research is the process of metastasis. This year, understanding of this deadly process has led to a new approach to block it. Recent work has shown that cancer cells spread by adhering to a protein, laminin, found on the lining of blood vessels. During the past year, small fragments of laminin have been prepared which can block the cancer cells' laminin receptor and so prevent attachment to laminin on the vessel's basement membrane. Laminin fragments have successfully prevented tumor cell spread in experimental animals. This novel treatment will begin clinical trials in patients this year.

Cancer biology has also shown that cancer cell proliferation is controlled by growth-promoting peptides and hormones. Human cells from small cell lung cancers produce growth factors that are capable of stimulating the cancer's own growth. Researchers have identified one of these growth factors, bombesin, and monoclonal antibodies have been designed against it. A novel clinical trial using these antibodies in patients with small cell lung cancer is under way.

Another new treatment approach, stemming from the discovery of growth factors in tumor cells, is the development of antibodies to the growth factor receptor itself. Monoclonal antibodies to the Interleukin-2 (IL-2) receptor of human T cells (white cells) have been linked to a potent toxin and have reduced tumors in the treatment of patients with T-cell leukemia. The antibody-toxin conjugates entered clinical trial for the first time last year and these studies will be expanded in 1986.

In clinical bone marrow transplantation experiments, monoclonal antibodies are also being used. Bone marrow transplantation allows higher and potentially curative drug doses to be given. The bone marrow, where blood cells are produced, is removed (from the patient or from a donor), stored during toxic treatment that could destroy it, and then placed back in the patient to restore damaged marrow. Monoclonals are being used to remove tumor cells from bone marrow stored from the patient, and to remove "killer" immune cells from bone marrow donated by another person because these could "attack" the patient's own tissues as foreign. In related research, a factor necessary for bone marrow development, Colony Stimulating Factor (CSF), has been purified and cloned, with potential for preventing bone marrow toxicity in patients who receive high-dose chemotherapy. In animals, CSF was used to synchronize bone marrow production before chemotherapy, then used again after treatment to reestablish safe levels of white blood cells.

Overall Budget Policy

Research Project Grants:

These levels will be achieved by limiting indirect costs and by negotiating direct costs downward. The request will support 874 competing project grants at an average cost of $170,561. This represents a 6.8 percent decrease in direct costs from 1986 and a 16.2 percent reduction from full recommended levels. Historically, these reductions have averaged three to four percent. The request will support 2,050 non-competing project grants at an average cost of $186,092. This represents a 5.1 percent increase in direct costs over 1986 and a 6.4 percent reduction from full commitment levels. Historically, these reductions have averaged one percent.

Centers:

The FY 1987 budget levels for cancer centers will be achieved by limiting indirect cost and by negotiating direct costs downward. The request will support a total of 57 centers. Non-competing centers will be reduced approximately four percent from commitment levels. This compares to a five percent reduction in 1986. Competing centers will be reduced 25 percent from recommended levels compared to a 20 percent reduction in 1986.

AIDS Research:

The request excludes $29,076,000 for AIDS, which are under the single AIDS appropriation in OASH. Comparable amounts for 1986 are $27,218,000 and for 1985 $26,874,000.

Last year, NCI made important contributions in many areas of AIDS research. These included advances in understanding the molecular biology of human T-cell lymphotropic virus-III (HTLV-III), the cause of AIDS; understanding the natural history and transmission of AIDS; identifying potential new therapies for the disease; and developing a vaccine and an animal model for the disease:

- HTLV-III was molecularly cloned and characterized, enabling scientists to study the different isolates of HTLV-III and to make direct comparisons of its sequence with that of other retroviruses.

- The entire genetic structure of the virus was mapped. From such analyses of HTLV-III and other retroviruses, scientists confirmed that the AIDS virus is a new virus in humans. With this map, or nucleotide sequence, scientists are now able to reproduce and analyze separately any structural part of the viral RNA by molecular cloning.

- A team of NCI and collaborating scientists demonstrated that a simple prototype blood test for HTLV-III antibody, similar to the tests that came into commercial use later in the year, is a reliable, specific, and sensitive tool for screening large numbers of blood samples for antibodies to HTLV-III. The study also reaffirmed the usefulness of such a test for initial screening for evidence of exposure.

- Major emphasis was placed on identifying and testing antiviral agents that may be effective against HTLV-III. During the past year, NCI screened over 120 agents for antiviral activity in tissue culture. These included anticancer drugs and immunorestorative agents such as interferon and Interleukin-2. Two agents, Suramin and azidothymidine (Compound S) are now in clinical testing. Several other agents will be taken through preclinical testing this year. NCI scientists believe a successful AIDS drug should be able to penetrate the blood-brain barrier. Many AIDS patients have unexplained dementia or degenerative disease of the brain which may be the result of HTLV-III infection of the brain.

- Neutralizing antibodies, or protective antibodies, were detected in some people who had been exposed to HTLV-III. The existence of the antibody shows that our bodies are able to respond immunologically to HTLV-III in a way that may lead to new prevention and treatment approaches.

- Scientists found extensive diversity in the genetic structure, particularly in the envelope genes, of different isolates of HTLV-III. The envelope gene protein on the outer coat of the virus is key to eliciting neutralizing antibodies. Consequently, variations in the envelope may mean that antibodies developed against one HTLV-III variant would not protect against other variants, making development of an effective vaccine more difficult.

- A vaccine development program has been initiated. The NCI s preparing a safe subunit vaccine that would contain only the viral proteins against which protective antibodies are made. The major virul glycoprotein, the target for antibodies which inactivate the virus, has been isolated in quantity. This subunit is being tested in animals and neutralizing antibodies have already been detected.

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National Cancer Institute

Research

1987 Authorization: Indefinite.

Budget Authority:

1986 Appropriation	Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$1,029,308,000	$984,216,000	$977,416,000	$970,890,000	-$6,526,000
		(FTEs: 1,901)	(1,903)	(+2)

Cancer Biology

Purpose and Method of Operation

Cancer biology research covers a broad spectrum of basic biological research in two major areas. One, tumor biology, advances our knowledge of the cellular and molecular factors which distinguish cancer cells from normal healthy cells and tissues. The other, immunology, focuses on determining the role of the immune system in controlling the development, growth and spread of tumors. Knowledge of these properties, processes and interactions are helping us learn how to prevent and counteract the biological signals responsible for the aberrant behavior of cancer cells. The most significant feature of basic cancer research is the emergence of unifying biological concepts from what once were considered diverse, unrelated areas of investigation. These unifying concepts bring together the most complex models for control of gene expression and cellular behavior, offering continued new opportunities and approaches for improving cancer prevention, diagnosis, treatment and the management of cancer patients. Basic research is rapidly providing improved tools for cancer diagnosis and prognosis and, more importantly, is setting the groundwork for the kinds of biological therapies which will markedly improve the effectiveness of cancer treatment.

Within the tumor biology program area are three major areas of investigation which correspond to different approaches of how to control the development and progression of neoplastic disease. The first is through understanding the basic biochemical mechanisms involved in growth control. Because cancer cells divide more often than most normal cells, many current therapeutic approaches to cancer are designed to kill dividing cells. However, cell division is a very complex process which begins with external cellular signals such as growth factors and ends with the expression of specific genes. Many of these genes have been identified and are called "oncogenes" because it is clear that their uncontrolled expression is responsible for neoplastic growth. Furthermore, the cooperation of several oncogenes is often required before tumors fully develop. The more we know about the different steps in the cell division process, the more specifically we can design chemotherapies and biological therapies that will be effective in both the prevention and treatment of cancer. The second approach involves studying changes that occur at the molecular and cellular levels which lead to cancer cell invasion. The invasive behavior of cancer cells is a prerequisite for malignancy, which is the ability of tumors to invade surrounding tissue, escape normal host defense mechanisms, including the immune system, and become established at multiple secondary metastatic sites of growth. Theoretically, if the invasive properties of malignant tumors could be controlled and these tumors confined to particular sites, metastasis, the major killer in cancer patients, would not occur. Therapies effective against localized cancer could be emphasized without fear of new growths beginning elsewhere in the body. The third approach is to develop detailed biological and biochemical information about the processes which induce cancer cell differentiation. There is good reason to believe that certain kinds of cancer will respond to external stimuli and differentiate into a normal type of cell. If the genetic program of an actively growing cancer could be changed to one of harmless terminal differentiation, the tumor would no longer be life threatening. Thus, through fundamental research in cancer biology, it is feasible to project that the therapeutic approaches of the future increasingly will involve agents designed to inhibit and/or prevent uncontrolled growth and invasion as well as agents which stimulate differentiation. Although the emphasis of tumor biology on growth, invasion and differentiation has been stated in simple terms, it provides a purposeful way of relating basic biological research to the ultimate goal of curing cancer.

Immunology, the study of the body's immune system, includes research on the role of this natural resistance mechanism in response to cancer as well as to infections and other diseases. The complexity of the immune system is becoming even more apparent as researchers better understand some of the disease-related consequences of Acquired Immune Deficiency Syndrome (AIDS), including the increased incidence of various malignancies. Basic studies of the immune defects of AIDS and other immune deficiency diseases continue to reveal the complexity of the functions and interactions of the component parts of this host defense system. The knowledge obtained from research in immunology is important to the understanding of cancer and its treatment in many ways: a) immune surveillance, i.e., how the normal immune system reacts to tumor cells; b) immune intervention, i.e., how a stimulated immune system assists the body in eliminating cancer cells or controlling tumor growth; and c) how our knowledge of the immune system can be used to generate diagnostic procedures and treatment modalities. Furthermore, cells of the immune system themselves may become malignant, resulting in the development of leukemias and lymphomas.

The immunology program is comprised of three major areas of research: 1) basic immunology; 2) tumor immunology; and 3) mechanisms of immunologic intervention. Basic immunology provides the background information on immunologic mechanisms which may involve immune cells and/or their soluble factors, including lymphokines and antibodies. Application of this basic knowledge to the study of tumor immunology - how the immune system recognizes tumor cells as foreign to the body - is a major research area in immunology. The surface of the tumor cell is the part of the cell that is exposed to attack by the immune system and may be affected by the expression of oncogene products. Immunologists are studying the effect of cell surface changes during tumor growth and metastasis to determine the nature of the altered surface components and the mechanism of their recognition by the immune system. Efforts are being made to translate new basic information and technology rapidly into clinical application that will improve the prevention, diagnosis and treatment of cancer. Monoclonal antibodies have proven to be extraordinarily valuable research tools, and many are being tested clinically, either alone or as drug, toxin or radionuclide conjugates, for diagnosis and treatment of cancer. Other soluble immune factors now being tested clinically and previously mentioned in this document include interferon, Interleukin-2 (IL-2) and tumor necrosis factor (TNF). Molecular biology techniques such as gene cloning are facilitating rapid availability of large quantities of newly-discovered immune factors for study.

There is no doubt that basic cancer research is in its most productive period of history. This is due in large part to the emergence of technologies that have become available for routine use in nearly all active scientific laboratories. Notable among these technologies is: 1) recombinant DNA technology, which utilizes discoveries such as restriction enzymes and the development of micro DNA sequencing methods, refining it to the point where nearly any gene and its controlling flanking DNA sequences can be cloned, altered and studied extensively; and 2) hybridoma technology which has been the hallmark for the development of monoclonal antibodies that can be tailored for use as tools of basic research or key factors in the diagnosis and treatment of cancer. The spin-offs of cancer research in the fields of human genetics and genetic engineering are likely to produce significant new results and approaches for curing other diseases. The possibilities for translating discoveries in basic cancer research to research in the clinic and then to general application grow more promising each year. There is no doubt that immunology and tumor biology research supported by NCI will yield major conceptual breakthroughs in our understanding of cancer processes and in our application of this knowledge to cancer diagnosis, treatment, and ultimately prevention.

Rationale for the Budget Request

The 1987 budget estimate of $241,857,000 represents a decrease of $4,264,000 from the 1986 estimate. The program plans for 1987 along with expected accomplishments, are as follows:

Tumor Biology - A 1987 estimate of $151,089,000.

Scientists are now able to isolate nearly any structural gene and its flanking DNA sequences. These sequences of DNA, which border each side of the gene coding for a functional protein product, represent the critical information that tells a gene how, when and where to be expressed. These flanking DNA sequences contain the most important information responsible for regulating normal gene expression or, when altered, producing aberrant gene expression as observable in cancer cells. It is now possible to make in the test tube combinations of different flanking DNA sequences and structural genes, inject these "foreign" genes into fertilized mouse eggs, and then observe the effect of different genetic combinations on mouse embryonic development and tumor expression. Much of cancer research in the past has focused on the use of cell lines in culture, which represent artificial situations. The use of the "transgenic" mouse model system offers incredible opportunities to observe how animal physiology responds to DNA constructs which have been specifically designed to produce tumors.

The flanking DNA sequences which border structural genes bind specific proteins that control gene expression. Until recently, the structural complexity of chromosomes and the limitations of analytical technology have been major obstacles to isolating and studying these rare proteins which control gene expression. Major breakthroughs in the use of recombinant DNA technology to clone flanking sequences and the development of methodologies for isolating these critical proteins offer new opportunities for studying and understanding the control of gene expression at the most refined levels of molecular biology and biochemistry. Because cancer is a disease of genes being expressed abnormally in the wrong place at the wrong time, it is crucial to maintain a strong commitment to the study of factors controlling gene expression in normal and cancer cells.

The biological activities of the products from oncogenes can be divided into a number of general classes: 1) those which can cause the transfer of phosphorus to a specific amino acid in proteins, i.e, tyrosine kinase activity; 2) those which have the ability to bind small nucleotide molecules which shuttle signals between the cell membrane and the interior of the cell to alter its metabolism; 3) those associated with growth factors or growth factor receptor activity; 4) those which exhibit DNA binding activity and are located in the nucleus; and 5) those which have unknown functions. Information on these various oncogene products has led to a number of models, all of which hypothesize the oncogene products are operating at different stages at one of a few common metabolic pathways. Major emphasis will be placed on developing a comprehensive molecular, biochemical and cellular understanding on the step-wise process of growth control. With this knowledge, it is expected that precise biochemical tools can be designed which will specifically inhibit the uncontrolled growth of cancer cells. New forms of biological therapies are expected to emerge from oncogene research which will substantially improve the effectiveness of treatment. Oncogene research is already is providing more effective tools for cancer prognosis and diagnosis.

A number of oncogene products appear to be proteins which have a specific biochemical modification as compared to their counterparts in normal cells. This observation suggests that there is the possibility of selectively altering the behavior of cancer cells by taking advantage of the knowledge of these specific modifications. For example, the products of the oncogenes erb-B and fms are defective receptor cell surface proteins which can no longer interact appropriately with their corresponding growth factors, Epidermal Growth Factor and Colony Stimulating Factor-1. Another modified cell surface protein, the product of ras oncogene, produces its transforming effects after one of a few very specific mutations has occurred that alters the structure and function of the normal ras gene protein. Increased emphasis to further understand specific biochemical modifications of oncogene products may provide critical information necessary to develop specific diagnostic methodologies, but more importantly, may provide the targets for monoclonal antibody therapy to directly eliminate tumor cells or to specifically deliver toxic chemicals and biologicals that can kill tumor cells.

Recent discoveries have established that Wilms' tumor and retinoblastoma occur because certain normal genes are missing or inactive in one chromosome of the parental genome. This means that children inheriting this defective chromosome from both the mother and the father will eventually develop cancer. These kinds of tumors clearly do not arise because of the activation of a transforming gene or oncogene, and the question must be addressed whether there are a significant proportion of cancers which develop when normal genes are not present. This is a particularly difficult problem to study because while it is simple to design experiments which demonstrate positive effects, such as those involving oncogenes, it is not easy to detect the absence of an unknown gene activity. Emphasis will be placed on identifying these unknown genes and determining how important this mechanism is for different forms of cancer. As more cancers of this type are identified and the biological functions of these missing gene products understood, we should not only gain critical information for understanding the mechanisms of growth control, but also be in a position to provide genetic counseling and screening that will reduce the occurrence of such cancers.

Increased emphasis will be devoted to understanding the process of gene amplification in cancer cells. By some unknown biological mechanism, cancer cells, but not normal cells, can produce many copies of the same gene, resulting in the over production of that gene's product. It is already well-established that this manner of overproducing a gene product can account for the acquired resistance of various tumors to certain kinds of drug therapies, allowing some cells in the tumor to continue to grow uncontrollably. In addition, it has also become apparent that many of the genes responsible for growth transformation (i.e., oncogenes) are amplified in different tumors, providing one explanation for how cancer cells overcome normal growth controls. The strong implication is that a variety of genes which code for functional products can be selectively amplified to promote the continued growth and survival of cancer cells. Thus, gene amplification is likely to be an important adaptive response which tumors can harness to resist chemotherapeutic drugs and thus progress to stages of greater malignancy. It has already been shown that increased amplification of the N-*myc* oncogene is linked to increased malignancy of neuroblastomas and that amplification of either the c-*myc* or c-*myb* oncogenes is associated with different subsets of acute myelogenous leukemias. There is every reason to believe that characterizing gene amplification in different tumors will lead to important new advancements in cancer diagnosis. More importantly, if clinicians can prevent the process of gene amplification from occurring during the use of conventional therapeutic regimens, the probability of tumor cells escaping the effects of toxic agents will be reduced and the survival of cancer patients increased.

Successful experiments over the last several years studying the mechanism of action of glucocorticoids have now firmly established the critical role of cellular glucocorticoid receptor in the regulation of certain protein production. This receptor binds specific DNA regions both within and outside the gene it affects. This research is important because of the widespread use of cortisone therapy which not only stimulates the synthesis of proteins but effectively kills certain types of cancer cells. Studies will continue to explain the specificity of this DNA binding and develop methods on how to enhance or interrupt it. The eventual outcome should be to eliminate harmful side-effects of this hormone or its chemical substitutes and to promote the beneficial effects in the cancer patient.

Now that the prototype for steroid hormone action has been established, similar work on estrogens and androgens can be accelerated. These sex steroids act as carcinogens in some target tissues and stimulate the growth of breast cancer and carcinomas of the uro-genital tract. Because these solid tumors are among the major cancer killers, it is imperative that new modes of therapy be developed. Understanding how the estrogen molecule attaches to the estrogen receptor and subsequently binds DNA sequence is of high priority with the goal of designing new anti-estrogens that will perturb any one of these steps. Once the active sites of the receptor protein are identified, we should be able to develop methods to interfere with those sites or to modify them to gain control over the growth of the tumor cells.

A number of growth and differentiation factors required for maturation of bone marrow stem cells into the heterogeneous array of blood cells have recently been purified and their genes cloned. Many years of support by the NCI for research on these "normal" growth factors, some of which are in fact produced by leukemia cells, has now been clearly justified as their potential use in cancer therapy is now becoming clear. Many of the genes for these factors have been cloned, resulting in the production of purified factors which may be used in a variety of ways. For example, granulocyte - macrophage Colony Stimulating Factor should be useful in protecting a patient's bone marrow stem cells for short periods of time so they are safe from the effects of toxic chemotherapy being administered to the patient. These same stimulating factors can also be administered to quickly re-establish a safe level of white blood cells in patients to help fight off infection after chemotherapy. Other Colony Stimulating Factors will soon be available in pure form for similar clinical testing.

There will be increased emphasis to study the properties and behavior of solid tumors. While they are much more resistant to experimental strategies compared to malignancies of the blood system, the opportunities for employing newer technologies are increasing and the animal model systems are improving. Special emphasis will be placed on understanding the cellular and molecular processes responsible for the growth of heterogeneous populations of cells within a given tumor. Finding the key factors which prevent new populations of cancer cells from arising would greatly increase the likelihood of developing effective treatment for those solid tumors which contribute the most to cancer mortality.

We will continue to emphasize the problem of metastasis and work to identify those characteristics of tumor cells which give them the special ability to survive throughout the metastatic process. The development of new model systems for this research is a high priority; one such new model is the demonstration of a stable mutant cell line derived from a human melanoma which then naturally metastasizes in nude mice. This has potential also as an experimental therapeutics model system.

One of the distinguishing characteristics of metastatic cells and currently under study is phenotypic instability, i.e., the ability to change characteristics. This has also been one of the major drawbacks in understanding the biology of metastatic cells. What controls the appearance and then disappearance of cell surface antigens and the new sudden expression of different genes, as is seen when these cells are cloned and maintained in culture, is under active study. Previously, it has not been possible to identify all the different cell surface molecules that could be used by a cancer cell. Now, however, the technology is available for the systematic experimental introduction into these cells of a gene, or genes, related to these surface molecules. Transmission of the associated characteristic to the cell represents a new approach to the problem that will begin to correlate aggressive tumor cell activity with the expression of specific molecules.

It is now clear that the extracellular matrix surrounding most cells exerts a strong influence over both the proliferation and the movement of those cells. Tumor cells frequently have either reduced amounts of, or an abnormal, matrix. The composition of this matrix includes very large glycoproteins such as fibronectin, laminin, actin, vinculin, collagen, and proteoglycans, which are responsible for cell-to-cell adhesion and recognition phenomena. Some of these macromolecules have been partially characterized but relatively little is known about the structure or function of the others. It is known however that they all lock into one another to form this complex matrix by specific binding sites and also attach to special receptor sites on the cells they surround. Fibronectin, for example, connects directly into the structural proteins within the cell that make up its cytoskeleton. The molecular basis for all these connections is being actively pursued in a number of laboratories. New antibodies against fragments of these matrix proteins and clever new reagents that fuse them at their respective binding sites will help provide a clear picture of how this extracellular matrix keeps cells under control. We should also being to understand how breakdown of the matrix allows malignant cells to detach from their home base and why they migrate where they do. As soon as more complete information is available on the natural extracellular matrix, it can be synthesized for use in cell culture. This may allow for the routine growth of solid tumor cells, the majority of which currently resist growth in culture and present major problems for the development of new diagnostic assays and for the investigation of drug sensitivity.

Immunology - A 1987 estimate of $88,227,000.

T cells are an important subset of lymphocytes which are involved in recognition and killing of tumor cells. The major breakthrough last year of the discovery of the structure of T-cell receptors has lead to explosive new developments in tumor immunology which will help to explain why cancer patients fail to mount an effective immune response against cancer. The newly discovered T-cell receptors are those molecules, present on the surface of T cells, which are responsible for the recognition of foreign antigens, and can thus discriminate between self and non-self (e.g., infectious agents) or altered-self components on cancer cells. Isolation and characterization of T-cell receptors and their genes have made it possible to discover errors in T-cell differentiation which may cause impaired resistance to disease. Studies on the aberrations in the structure and arrangement of T-cell receptor genes have opened up new vistas in the classification, prevention, diagnosis, and treatment of certain types of lymphomas and leukemias. Studies of chromosomal localization of T-cell receptor genes will help to understand the mechanism of neoplastic transformation of normal T cells. Characterization of T-cell receptors and associated structures will help to further delineate subsets of T cells such as T4 cells, the depletion of which is responsible for the development of AIDS. The availability of cloned T-cell receptor molecules will permit studies on the nature of physical interactions between the receptor and antigen, which are needed to clarify the enigma of restricted antigen recognition and the molecular aspects of antigen presentation. In addition, research will focus on the use of hybridoma antibodies and immunotoxins specific for T-cell receptors and associated molecules to target drugs to malignant T cells.

It is well known that cytotoxic T-lymphocytes recognize foreign antigens only in association with the appropriate major histocompatibility complex (MHC) antigens. Recently, gene transfection has been used to restore MHC antigen expression to metastatic tumor cells which lacked this expression, resulting in reduced tumor growth and loss of metastatic properties. This finding is important because some human cancer cells have been found to have decreased levels of MHC antigen expression on their surface resulting in the lack of recognition by the immune system. Efforts will be focused in this area to explain the role of aberrant MHC expression in the emergence and progression of cancer. Also, strategies will be developed to enhance MHC expression on cancer cells, thereby increasing their susceptibility to destruction by the immune system.

In addition to their recognition and cytolytic (cell destruction) functions, T cells also regulate the function of other cell types such as B-cells and macrophages, thus coordinating various arms of the immune system. Some of these regulatory effects are communicated by direct cell-to-cell interactions, others by the release of soluble mediators called lymphokines, which are proteins which transmit growth and differentiation signals among immune cells. The genes of several lymphokines, e.g., IL-1, IL-2 and various types of interferons, have been cloned, permitting the preparation of these important substances on a large scale useful for clinical study. Recently, the genes of two related substances, tumor necrosis factor (TNF) and lymphotoxin (LT), have been identified and cloned. These factors are extremely toxic to some tumor cells, especially in combination with interferon.

Further studies of lymphokines, TNF and LT will focus on the mechanisms of normal and abnormal responses of immune cells, leading to improved therapeutic modulation of the immune system. Several of these factors, such as IL-2, gamma interferon and TNF, are already being tested clinically for their antitumor effects in cancer patients. Large quantities of purified factors are also needed to grow immune cells with antitumor activity in culture. These cells, when transferred into an animal or patient, can mediate an antitumor immune response in the recipient. Promising initial results have been obtained by treating cancer patients with lymphokine-activated killer (LAK) cells. In this procedure, lymphocytes taken from the patient are activated in culture with IL-2 and returned to the same patient along with additional IL-2 (See Treatment Section). Further studies will include other immune cell types, such as natural killer (NK) cells augmented with interferon, cytotoxic T lymphocytes activated with IL-2, or macrophages armed with monoclonal antibodies. In order

To develop a solid foundation for clinical applications, efforts will focus on determining the mechanisms of action of soluble factors and stimulated immune cells in the eradication of cancer cells.

Monoclonal antibodies continue to be a major tool for basic cancer research, contributing to studies of the cell biology and immunology of cancer. Currently available monoclonal antibodies are being used to assess the degree of heterogeneity in individual tumors. As new monoclonal antibodies become available, they will facilitate more accurate and detailed diagnosis and classification of tumors. Additional monoclonal antibodies are needed to study the expression of oncogene products on the surface of tumor cells, and to study the relationship of newly defined cell-surface components to tumor-associated antigens which are recognized by the immune system. These studies are important for understanding the mechanism of the immune response to those tumor cells which express oncogene products on their surface, and the studies will contribute to the development of improved diagnostic procedures.

Research is continuing to develop better methods for the specific delivery of monoclonal antibodies for improved diagnosis and treatment of tumors. New procedures are being tested for the conjugation of monoclonal antibodies to drugs, toxins or radionuclides, and alternative routes of antibody-conjugate administration, including the use of liposomes as carriers, are being investigated (See Treatment Section). Research is continuing on the development of human monoclonal antibodies to avoid the possibility of adverse reactions to antibodies produced in other animal species.

An innovative approach to the stimulation of active specific immunity involves the use of anti-idiotype antibodies as immunogens. Anti-idiotype antibodies are in fact the mirror image of the specific binding site of the original antibody, and therefore, can mimic the original antigen in eliciting an immune response from the host. These studies of anti-idiotype antibodies are important because this technology can provide a more effective and safer way of inducing active immunity, completely bypassing the need to inject potentially pathogenic material as a vaccine. This approach may be particularly important in the development of a vaccine to protect against AIDS. In addition, these antibodies will be important for basic research because they will be useful tools for the isolation of molecules, such as various receptors, which are difficult to purify.

Bone marrow transplantation has shown increasing promise for the reconstitution of the immune system following high doses of chemotherapy and/or radiation. However, this treatment has been limited by the complications of engraftment failure or graft-versus-host disease (GVHD) which often follows transplantation of bone marrow from a donor. Monoclonal antibodies have been used to eliminate the T-cell subsets which cause the GVHD. Effort will be focused on more detailed studies of the engraftment process, with emphasis on reconstitution of immunologic function, in order to better understand the contribution of the various cell subsets to either the engraftment process or GVHD. Monoclonal antibodies will be used to remove any tumor cells which may have metastasized to the patient's bone marrow, thus allowing for the use of the patient's own bone marrow for later transplantation to rescue the immune system following intensive chemotherapy/radiotherapy for treatment of solid tumors. In addition, research will continue in the development of new immunosuppressive agents and in the investigation of their mechanism of action to order to improve the potential of organ and bone marrow transplantation in the treatment of cancer.

The HTLV-III virus has been identified as the causative agent of AIDS; however, much remains unknown about the pathogenesis of this disease. It is still unclear what, if any, cofactors contribute to the various manifestations of AIDS, and what factors lead to the development of the particular types of cancer which are seen with increased frequency in AIDS patients. Development of a clinical test for the anti-HTLV-III antibodies in serum has facilitated rapid testing for an individual's exposure to HTLV-III. Test results indicate that many people without symptoms of the disease have been exposed to this virus and have developed antibodies. It is now necessary to determine what specific immunologic mechanisms are effective in controlling the progression of AIDS. This information is essential for the development of effective vaccines. Additional monoclonal antibodies will be developed to further analyze the development of the specific immune defects, to monitor closely the distinct steps in disease progression, and to determine the potential to reverse the course of the disease at various stages. The factors leading to the development of the unusual spectrum of malignancies (including Kaposi's Sarcoma) in some but not all AIDS patients, and the cell of origin of Kaposi's Sarcoma, will be investigated. Improved immunologic methods to detect HTLV-III infection before the onset of irreversible immune deficiencies will be emphasized.

Although researchers generally agree that the immune system plays a significant role in the prevention and/or control of tumor cell growth, there is disagreement regarding which subset of immune cells is most effective against tumors. The use of monoclonal antibodies has demonstrated the heterogeneity of antigen expression on the tumor cell surface, which may contribute to a difference in susceptibility to immunologic destruction. Research will strive to increase the effectiveness of the immune system for tumor cell killing. More studies are needed to explain the role of soluble factors, including antibodies, in immune surveillance, to determine how cytotoxic lymphocytes and macrophages kill tumor cells, and why, in certain forms of cancer, they fail to function effectively. The new basic research findings on T-cell receptors, MHC antigens, and the mechanism of action of cytolytic cells will be applied to develop methods to mobilize the host's immune system against cancer cells. Efforts will be focused on the effect of environmental factors, diet and nutrition on the immune system, as well as on the interactions of the nervous, endocrine and immune systems. Understanding the effect of external factors on the immune system's ability to function in surveillance against cancer is of great importance for cancer prevention, and research efforts in this area will continue.

Nutrition - A 1987 estimate of $2,541,000.

Basic research on nutrition includes a spectrum of projects involving cell biology, genetics and biochemistry. The importance of lipid biochemistry in the synthesis of membranes for new cells, both normal and malignant continues to be a major emphasis. The involvement of lipids is also critical in a pathway of gene regulation recently identified that involves the phosphorylation, and thus

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activation, of important molecules. The role of cellular concentrations of calcium and its rate of flux from one cell compartment to another is also now implicated in gene regulation and the ability of cells to grow. How calcium and other ions effect the activity of large proteins is an especially intriguing question. The long observed high rate of glucose oxidation in cancer cells, as compared with normal cells is also receiving new attention. Evidence suggests that modification of certain enzymes or their receptor proteins on subcellular structures makes glucose utilization more efficient in the tumor cells.

Cause and Prevention Research

Purpose and Method of Operation

Human cancer appears in the great majority of cases, to be a disease which develops over a period of many years. Although the early cellular and molecular events related to cancer causation are not completely understood, the neoplastic process appears to progress through several stages of development and a variety of factors can act to affect its development at each stage. At present, scientists separate this process into two distinct stages. The first stage, "initiation", generally occurs as a consequence of exposure to substances that damage DNA, the cell's hereditary material. The second stage is called "promotion" and generally requires a longer exposure time than does the initiation stage. Initiators include chemicals, fibers, radiation and viruses. Nutritional, hormonal, environmental, and genetic factors can act as promoters. Promoters do not cause cancer directly; they facilitate the carcinogenic process.

In human cells in tissue culture as well as in animals and humans one or more enzyme systems may be required to activate a chemical to its carcinogenic form, called the ultimate or proximate carcinogen. Current evidence indicates that one of the earliest events in the process of carcinogenesis involves a structural change in the DNA of a target cell caused by this ultimate carcinogen - a point mutation or perhaps more generalized damage to DNA - prior to its transformation into a cancer cell. Significant interactions may also occur outside the nucleus, in the cytoplasm or at the cell surface. Nevertheless, it is possible that the carcinogen-bound or damaged DNA can be repaired, and the failure or inability to repair this damage may be linked to a propensity to develop cancer. If unrepaired, the damage may result in the activation or "turning on" of an oncogene; this in turn could cause increased production of a gene product which in some way regulates or controls cell growth and differentiation and may be responsible for maintaining the transformed (malignant) state. Finally, there may be other factors required for transformation to malignancy. Understanding the mode of action of tumor promoters is an important goal in cause and prevention research, because there is evidence that removal or interference with the action of tumor promoters may be the simplest way of reducing cancer incidence. Although many of the details of the stages of cancer development remain to be elucidated the existence of such a chain of events offers the possibility that it may be interrupted at various points. Indeed, one of the primary tenets of cause and prevention research is that if enough can be learned about the specific molecular mechanisms which cause a normal cell to become malignant, ways can be found by which cancer can be prevented or reversed.

Cause and prevention research recognizes the interrelationships among factors which initiate and promote cancer including external influences, host factors, and the genetic endowment of the individual. Consequently it includes investigations into chemical and physical carcinogenesis, biological carcinogenesis, epidemiology, chemoprevention and nutrition. Each of these scientific areas interacts with the other: epidemiology attempts to identify environmental and genetic risk factors; chemical and physical carcinogenesis research seeks to elucidate the specific molecular ways in which chemical and physical agents trigger malignancy; biological carcinogenesis research, using viruses and defined DNA sequences as investigative tools, examines and analyzes the genes and gene products which can cause cancer; chemoprevention research aims to identify chemicals and other agents capable of preventing or reversing the process of carcinogenesis at one or more stages; and nutrition research attempts to identify foods, nutritional factors, and dietary habits that may either induce, promote or inhibit cancer. Research findings in any one of these areas may shed light on a problem being investigated in another, for ultimately each discipline is concerned with the fundamental causes and prevention of human cancer.

In the area of biological carcinogenesis, fields of active research include DNA containing viruses, RNA tumor viruses (retroviruses) and studies on oncogenes. The papillomaviruses are DNA viruses which are associated with naturally-occurring tumors and experimentally induced tumors in a variety of animal systems. Further, evidence is mounting which associates human papillomaviruses with precancerous and cancerous lesions of the anogenital tract, and DNA from human papillomaviruses has been isolated not only from human cervical carcinoma specimens, but also from metastatic deposits in lymph nodes from the same patients. Research on the progression of the disease from primary infection to dysplasia or carcinoma will be carried out, and studies to determine the natural progression and transmission of infections are underway.

RNA tumor viruses are unique among animal viruses in their mode of transmission and the intimate association that has evolved between these agents and the cells of a large number and wide variety of vertebrate species. The etiologic role of this virus group has been established for naturally-occurring cancers of many species, including some non-human primates. Certain members of this virus group, known as "replication-defective" transforming viruses because they have deleted the gene required for them to reproduce, have arisen by a recombination with cellular genes or proto-oncogenes. As such, these viruses offer an unparalleled opportunity to clarify the process by which such genes cause tumors, and research to elucidate these processes in malignancy is actively being pursued utilizing RNA tumor viruses as models. Recent investigations have provided strong evidence that proto-oncogenes are frequent targets of genetic alterations leading human cells along the pathways to malignancy. Much current research is aimed at identifying oncogenes in human cancer, their molecular mechanisms of action, and how their protein products function in neoplasia. Recent studies have also demonstrated that the activation or "turning on" of oncogenes may be an essential component of the process of chemical carcinogenesis.

Studies in the area of chemical and physical carcinogenesis are increasingly mechanistic in nature. Recent studies have identified two different oncogenes in chemically-induced tumors of rats: oncogenes of the ras family were found in kidney tumors; and tumors of the peripheral nervous system contained an oncogene of the erb-B family. Thus it appears that specific oncogenes may be expressed in specific types of chemically-induced tumors. This exciting observation exemplifies how the fields of chemical and biological carcinogenesis are converging and provides additional evidence that carcinogenesis is a multi-step process: chemical carcinogens may produce tumors by interacting with DNA in such a way as to either activate oncogenes or inactivate the regulatory elements that control oncogene expression. The subsequent proliferation and uncontrolled growth which characterizes cancer may reflect the overproduction of a normal oncogene product or the production of an abnormal product.

Other studies will examine the interaction of chemical carcinogens with DNA, the repair of DNA damage induced by chemicals and by physical agents including asbestos, ultraviolet radiation and X-irradiation and how the genetic constitution of individuals affects the extent, efficiency and fidelity of the repair process. Studies on tumor promotion will continue to be emphasized and will be carried out at the molecular level, as well as in *in vitro* and *in vivo* model systems. Similarly, studies on growth factors such as transforming growth factor-beta (TGF-beta) and on lymphokines such as leukoregulin will be emphasized since these endogenously produced substances appear to play a modulating role in tumor progression and tumor growth. Laboratory techniques will continue to be refined to allow epidemiologists to better characterize exposure to carcinogens, to assess specific host susceptibility status and to measure early biochemical responses to carcinogens.

Traditional epidemiologic studies sought to identify environmental and genetic risk factors and such studies provided valuable "leads" for subsequent analytical epidemiologic studies as well as for laboratory studies on causality and mechanism. More recently, with the development of sophisticated new laboratory techniques and their incorporation into epidemiologic studies, it has become possible to identify cancer risk factors on an individual in addition to a population basis. The remarkable progress which has been made in the last four years on identifying HTLV-III as the etiologic agent for AIDS, defining the characteristics of members of high-risk groups and increasing our understanding of viral transmission could have been made only through the close interaction between the epidemiology and biological carcinogenesis programs. Similarly, biochemical probes developed in the chemical carcinogenesis program are being applied as monitors of exposure in epidemiologic studies of environmental and occupational carcinogenesis. The merging of these fields of epidemiology with those of chemical and biological carcinogenesis has opened a new area of research referred to as biochemical or molecular epidemiology. Such biochemical probes may prove to be particularly valuable when applied to nutrition research.

In the nutrition program the focus is on the identification of foods, nutritional factors and dietary habits that are able to either cause or prevent cancer; a component of this program is chemoprevention research in which the objective is to identify chemicals and other agents which are capable of preventing or reversing the process of carcinogenesis at its later stages. The application of biochemical epidemiology to studies of diet and cancer is particularly timely; important studies are underway in which the relationship between common cancers (e.g., lung, breast, colorectal) and dietary factors including micronutrients (e.g., vitamin A and trace metals) and macronutrients (e.g., dietary fat and fiber) are being defined. Such studies should be useful in identifying populations and individuals at high cancer risk for recruitment into intervention and prevention trials.

An important new development in nutrition research actually originated in the chemical carcinogenesis program: the detection and identification of dietary mutagens. Some of these chemicals, known as heterocyclic amines, are formed when food (especially meat) is subjected to high temperatures in the cooking process; another class of these chemicals (known as fecapentaenes) are formed endogenously by the bacteria which are normally present in the intestine. These chemicals are generally very potent mutagens and several of the heterocyclic amines have been demonstrated to be carcinogenic in rodents. The fecapentaenes are currently being examined for carcinogenic potential in laboratory experiments. The fecapentaenes have been found in feces from individuals at high risk for colon cancer and thus may be implicated as a causative agent for colon cancer. Biochemical epidemiologic studies will pursue the origin, synthesis and carcinogenic potential of dietary mutagens in populations at high risk for colon and other types of cancer.

Rationale for the Budget Request

The 1987 budget estimate of $285,733,000 represents a decrease of $2,586,000 from the 1986 estimate. The program plans, along with expected accomplishments, are as follows:

Chemical and Physical Carcinogenesis - A 1987 estimate of $108,309,000.

The development of several forms of cancer appears to occur in at least two steps: the initiation stage and one or more promotion stages. The initiation stage involves the interaction of a chemical with DNA in such a way as to alter its function. A single exposure can be sufficient to induce the initiated state, and this state may be irreversible. The development of techniques to maintain human cells and tissue under chemically-defined culture conditions for prolonged periods has been an important advance in carcinogenesis research because now researchers can study at the cellular and even molecular level many phenomena believed to be critical to initiation and the early stages of tumor formation. These phenomena include the metabolic processing of a chemical (procarcinogen) to its active carcinogenic form, the interaction of that chemical with important cellular constituents (e.g., DNA, RNA and proteins) - the products of such interactions are known as adducts - the damage to DNA that can occur as a consequence of adduct formation and the repair of that damage. The importance of being able to maintain cells in chemically-defined media is that now researchers can study the complex interactions which take place between various growth factors, chemical carcinogens, anticarcinogens (e.g., retinoids), and the cell. Such studies will be pursued with vigor during the coming year.

Information as to how and where carcinogens interact with DNA can provide clues as to the mechanism by which the carcinogen exerts its biological effects. Therefore efforts to identify, quantify and characterize carcinogen-DNA adducts in biological systems will be continued. Very sensitive immunologic techniques have been developed to detect carcinogen-DNA adducts in individuals exposed to environmental carcinogens such as benzo(a)pyrene and aflatoxin B. Antibodies to carcinogen-DNA adducts have also been detected in sera from people exposed to benzo(a)pyrene. Due to the longevity of immunological memory, such antibodies may be useful as an indicator of exposure to carcinogens which occurred many years previously. Whether or not these antibodies will be a useful indicator of cancer risk is being assessed. Recently, immunological probes have been developed and utilized to monitor patients receiving cancer chemotherapy. The primary mechanism of action for the cytotoxicity of certain cancer chemotherapeutic agents is binding to DNA, and specific antibodies have been generated against the major binding product of the antitumor agent cis-platin and DNA. This extremely sensitive technique is now being used to monitor cis-platin chemotherapy. Preliminary results indicate that levels of cis-platin adducts increase with increasing dose and duration of therapy and that clinical response is significantly greater in those patients in which highest adduct levels are found. Conversely, patients who fail to form adducts during therapy have a poor response record. This unique methodology, which developed from experiments in basic carcinogenesis research, provides a promising new predictive test for chemotherapeutic response. It also provides a tool to monitor improvements in therapeutic modalities for patients undergoing cancer treatment. During the coming year, this approach will be broadened to develop and employ additional immunologic reagents for this purpose.

A group of enzymes, the mixed function oxidase system, represents the primary interface between environmental chemicals and human beings. The cytochromes P450 are a major component of this system. These enzymes are important because, as receptors for foreign chemicals, they are responsible for detoxifying or inactivating a wide variety of drugs, carcinogens and other environmental agents. They are also important because they have the ability to transform some types of chemicals (procarcinogens) into active carcinogens. Whether or not a chemical is carcinogenic is determined, to some extent, by the balance between detoxification and activation. For a given chemical, this balance can vary according to species, sex, hormone status, previous chemical exposures and a number of other factors. Monoclonal antibodies to various forms of cytochromes P450 have been prepared; soon they will be applied to the identification of individuals at increased risk of cancer either because they have a below-normal ability to detoxify chemicals or an enhanced ability to activate procarcinogens.

Tumor promoters, in contrast to tumor initiators, do not appear to interact with DNA; recent studies suggest that they act by modulating gene expression, growth and differentiation. By themselves they are not able to produce tumors, but they markedly enhance the formation of tumors when applied after exposure to an initiating agent. Multiple exposures to a promoting agent are generally necessary to be effective, suggesting that promotion is a reversible phenomenon. Tumor promotion has been demonstrated in in vitro systems and in experimental animals and there is reason to assume that it plays a role in human cancer as well. An important recent observation has been made with one such promoter, a chemical known as TPA (12-0-tetradecanoyl phorbol-13-acetate). The cellular receptor for this and probably other promoters belonging to the same chemical class has been identified as the enzyme protein kinase C. The enzyme has been purified and features of its biologic function have been clarified. This work has shown that protein kinase C is a critical regulator of cellular growth and differentiation and is an important intermediate in the tumor promotion process. These studies will be expanded since they will provide a focus for determining important events in chemical carcinogenesis and critical factors which determine the cellular response to tumor promoters.

An exciting new development which took place during the past year is the finding that the DNA of tumors induced in animals by a single exposure to a type of carcinogen known as an alkylating agent contains oncogenes. Two different genes belonging to the ras family of oncogenes were identified and isolated at high frequency from primary kidney and nasal cavity tumors. Chemically-induced tumors of the peripheral nervous system (called Schwannomas) have been found to contain an oncogene belonging to a different group, the erb-B family. The demonstration of specific associations between activated oncogenes and chemically-induced tumors suggest a commonality in mechanism for chemical and viral carcinogenesis, and future studies will further explore this possible relationship.

Studies on dietary mutagens will remain an important area of research. Interest in this area is focused on two distinct groups of chemicals. One group, known as the fecapentaenes, are potent mutagens and their presence in human feces correlates with risk for colon cancer. These mutagens are produced by the bacteria that normally are present in the intestinal tract. Recently the methodology to produce relatively large quantities of one of these chemicals, fecapentaene-12, was developed, and its availability to the research community has stimulated studies of its carcinogenicity and mechanism of action in animals. Originally shown to be mutagenic in bacteria, fecapentaene-12 has now been shown to produce mutations in mammalian cells and to induce single strand DNA breaks in cultured human cells. Tests of its ability to serve as a "complete" carcinogen as well as an initiator of the carcinogenic process in experimental animals are underway. If positive, efforts will also begin to develop strategies for blocking the effects of these substances in the colons of animals. Future studies will also pursue the origin, synthesis and carcinogenic potential of the fecapentaenes in human populations at high risk for colon cancer. Valuable leads for prevention have been provided by the observation that bacterial production of the fecapentaenes is enhanced by bile and reduced by fiber. The second class of dietary mutagens, the heterocyclic amines, are produced when human food, particularly meat, is subjected to high temperatures during cooking. These substances, too, are potent mutagens and preliminary studies of carcinogenicity in rodents indicate that they are capable of inducing tumors at various sites including the intestine. Research on the mechanism of action of this new class of mutagens will be expanded and efforts made to develop procedures to block their formation or inactivate them once formed.

Continued emphasis will be placed on chemoprevention research during the coming year. Chemoprevention refers to the administration of chemical agents to prevent the sequence of events that follows the exposure of an individual to a carcinogenic agent and results in the development of a malignancy. It involves the introduction of selected micronutrients, both synthetic and naturally occurring, or other small molecular weight substances into the diet for the purposes of reducing cancer incidence. The areas of emphasis in chemoprevention will be as follows: (a) Identification and evaluation of compounds showing biological activity in experimental systems. Such studies are continuing, utilizing in vitro and in vivo systems; (b) Synthesis of more potent and/or less toxic compounds. Success in this direction could come from the synthesis of compounds of greater intrinsic activity or more selective organ distribution, i.e., site monitoring; (c) Initiation of additional dose-setting and controlled clinical trials in chemoprevention. For example, several synthetic retinoids have shown striking effectiveness at specific sites in animal models. Success in this area would greatly stimulate further studies and; (d) A number of short term biochemical and biological markers i.e., atypical cytology, dysplasia, micronuclei, precancerous conditions, fecal mutagens, and oncogene suppression tests are becoming available and might be used in conjunction with, and evaluated during, a clinical trial. Trial designs can be improved by methods utilizing these tests to initially predict cancer risk or its modulation. Evaluation of the biochemical marker will also be conducted concurrently with the clinical trial.

A variety of in vitro systems are being used to evaluate the activity of chemopreventive agents. Effects on cell lines of both epithelial and fibroblastic origin are being evaluated and integrated with the chemopreventive agents ability to inhibit cellular transformation. In vivo screening systems are continuing to provide information on the activity of chemopreventive agents in assays which measure inhibition of tumorigenesis. The results of these initial screening assays will be used to select the agents that will be further evaluated in a larger panel of animal models for efficacy.

Preclinical studies of the toxicology of chemopreventive agents are being implemented to evaluate their acute, subacute/subchronic and chronic toxicity. These studies will be performed in animals and will include conventional short-term studies, life-time studies in rodents, and multi-generation teratogenicity studies. Agents to be evaluated include selenate and selenomethionine. Phase I human clinical trials to evaluate toxicity and safety of agents under consideration as potential human chemopreventive agents are continuing. Studies of beta carotene have been completed and studies with selenate and selenomethionine will be implemented.

A new approach to cancer prevention, National Collaborative Chemoprevention Projects, will be initiated during the coming year. These collaborative projects are designed to acquire basic knowledge in significant biological systems for anticarcinogenesis. A multi-disciplinary approach is being employed in order to derive new insights into practical means for prevention of the process of carcinogenesis and to translate this knowledge rapidly into new chemopreventive entities with known ranges of efficacy and defined pharmacologic/toxicologic properties.

A peptide growth factor, transforming growth factor-beta (TGF-beta) has been characterized and purified. The peptide was named for its ability, in concert with another growth factor, to transform normal cells into malignant ones. However, it has recently been shown that TGF-beta can actually inhibit the growth of some tumor cells. Human platelets have been identified as a major source of TGF-beta; they contain 100 to 1,000-fold more of this peptide than do other cells which have been examined. The gene for TGF-beta has been cloned and its complete amino acid sequence determined. There is recent evidence that TGF-beta plays an intrinsic role in inflammation and tissue repair, and extrinsic TGF-beta can stimulate the formation of connective tissue and collagen in animals. In another series of experiments it was demonstrated that TGF-beta injection stimulates the formation of new blood vessels, a phenomena known to occur during the growth of a solid tumor. These results have important clinical implications and studies on this and other growth factors will be expanded during the coming year.

Studies of biologic events in bladder cancer, e.g., on initiation, promotion, and invasion, need to be pursued in addition to the current emphasis on chemical events. These studies would include differentiation-dedifferentiation, tumor angiogenesis and epithelial-stromal relationships and interactions. Macromolecular interactions with carcinogens will be studied at a mechanistic level including studies to determine the loci associated with carcinogen induced expression of oncogenes. Oncogene expression and stromal-epithelial interactions will also be studied in breast and prostatic cancer. Chemoprevention will be studied particularly with reference to micronutrient interactions in the prevention of experimental mammary cancer. In addition, there is a need to follow up findings suggesting a gene for susceptibility to breast cancer linked to a known marker on the human chromosome. Also, factors influencing susceptibility of the breast to carcinogenesis and the biochemical mechanism of initiation will be examined.

The means by which exposure to ionizing and non-ionizing radiation, particularly at low doses and dose rates, leads to molecular events and processes resulting in mutagenesis, cell transformation and carcinogenesis continues to be an area of active investigation. These studies, carried out in biological systems ranging from yeast to bacteria to human cells, are directed at defining dose-response relationships, assessing DNA damage and repair following radiation exposure, mutagenicity-carcinogenicity relationships following exposure to radiation, interspecies comparisons, and interactions among co-carcinogens. These basic biophysical and radiochemical investigations are being complemented by epidemiologic studies. For example, efforts are underway to develop a valid assessment of the risks of thyroid doses of I131. Methods to estimate the thyroid doses of I131 that were received by individuals from nuclear weapons fallout are being evaluated and the degree of exposure to I131 that individuals received following the Nevada atmospheric nuclear bomb tests is being assessed. Research emphasis in the coming year will be directed at clarifying the possible interaction of radiations with oncogenes, studying the sensitivity of the embryo and fetus to ionizing radiation, evaluating the effect of dose rate and linear energy transfer on radiation-induced effects, and determining the incidence of selected diseases as they may relate to exposure to radioactive fallout. Such activities are crucial to the synthesis of radiobiological data in the assessment of risk and the establishment of appropriate radiation protection practices.

Biological Carcinogenesis - A 1987 estimate of $103,720,000.

Remarkable advances in knowledge and technology related to molecular biology have been made during the past few years and these advances are being applied to studies of biological carcinogenesis. In particular the new findings and concepts arising from molecular biology have produced a resurgence of interest in viruses as a cause of human cancer. The new technologies have made it possible to identify in human cancer cells specific oncogenes originally isolated from rodent and avian viruses. A relatively small number (about 30) of the normal cellular counterparts of these genetic sequences, termed proto-oncogenes, seem to be present in all human cells and it is thought that they code for important cellular functions such as differentiation. It appears that their modification or activation may be responsible for the transformation of normal cells into malignant ones.

This possibility has served as an impetus for efforts to identify additional oncogenes, to understand what purpose oncogenes serve in the normal cell, how oncogenes are activated and to compare normal and abnormal oncogene products to determine at which stage abnormalities occur. Large amounts of cloned oncogene products can now be produced and efforts will be focused on determining their structure, active site and biological activity. The development of strategies for preventing or treating cancer may depend upon agents which interact with targets present only in cancer cells and essential to their proliferation and survival. Oncogenes and their products may represent precisely such a target. By gaining a better understanding of oncogenes and the products they encode, it may be possible to antagonize their function to prevent cancer.

HTLV-I virus is now considered the direct causative agent for some human cancers, based on the very strong epidemiologic association of the virus with adult T-cell leukemia and its repeated isolation from patients with cutaneous T-cell leukemias and lymphomas. Studies on HTLV-I and a related virus (HTLV-II) will be expanded in order to elucidate fundamental phenomena such as the mode of virus transmission, virus-host cell interactions, and the molecular basis of virus transformation by two members of this important group of human retroviruses.

The identification of HTLV-III as the etiologic agent for AIDS by an NCI scientist was an important breakthrough because it has made it possible to develop an effective screening test to help protect the nation's blood supply. In addition, it has permitted efforts to begin to develop an effective vaccine for high-risk individuals. It has been found recently that HTLV-III has certain properties in common with HTLV-I, HTLV-II and bovine leukemia virus. The similarity concerns the way this group brings about the enhancement of their own growth (and eventually the death of host cells) through a transacting factor, probably a protein, which is coded for by the virus' own genome. Thus, HTLV-III seems to belong in the same retroviral family that includes HTLV-I, HTLV-II and bovine leukemia virus, all of which are associated with neoplastic disease and which bring about a similar autostimulation of their own growth and the malignant behavior of infected host cells through transacting proteins. Another recent observation regarding HTLV-III is that it is similar to several other retroviruses of domestic animals. These viruses are "slow" viruses belonging to the lentivirus subfamily of retroviruses and they all affect cells of the immune system. Despite differences in the outcome of infection by various lentiviruses, there is an important point in common: once infected, individuals remain infected for life. Lentiviruses, like other retroviruses, can integrate into the hosts DNA and remain there as long as the cell is not killed by the virus, eliminated by the host immune system, or removed through senescence. Lentiviruses have developed different strategies to evade elimination by the host's immune system. For some, apparently including HTLV-III, they do so by a process called "genetic drift" in which changes in the genes controlling the composition of their outer coating produces variants which escape immune detection, and the viruses are able to induce a new cycle of

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disease. Studies during the coming year will be aimed at obtaining a better understanding of the mechanism of lentivirus persistence in order to expedite the development of an effective vaccine against HTLV-III.

New areas of research on retroviral vaccines will be stimulated, including development of naturally-occurring retrovirus animal models to systematically evaluate strategies for vaccine development and assessment; basic studies to determine how retroviruses interact with the host immune surveillance system; and utilization of newer methodologies to produce and evaluate retroviral vaccines.

Studies on feline leukemia virus (FeLV) will be emphasized. FeLV is responsible not only for malignant diseases, such as leukemia and lymphosarcoma, but also causes other serious diseases of cats such as anemia, immunosuppression, and reproductive failure. In this respect a parallel exists between FeLV and HTLV-III. Thus FeLV offers a potentially useful and important model of oncogenesis/immunodeficiency syndrome in an outbred species and studies on the biology, immunology, and molecular biology of FeLV should provide important information about HTLV-III.

A fatal immunodeficiency disease similar to human AIDS has been observed in a colony of Rhesus monkeys, and investigators have isolated a retrovirus from the diseased animals which is serologically related to HTLV-III. The virus, termed Simian T-cell lymphotropic virus III, was demonstrated to be capable of transmitting the immunodeficiency disease from monkey to monkey. These results provide important insights into the natural distribution and pathogenicity of these related viruses and may even suggest the possible origin of HTLV-III from monkeys. More importantly, the existence of this new AIDS-like animal model will facilitate the development and testing of possible vaccination and therapeutic approaches to AIDS in a readily available primate.

Studies on other exogenous and endogenous human retroviruses will be initiated. Multiple uncharacterized human type-C viruses and endogenous proviruses may represent a potential source of infectious retroviruses, and by analogy with animal model systems may serve as a potential source of new human cancer viruses. Knowledge and availability of newly developed technologies and methods, such as the use of growth factors for cultivation of T-lymphocytes, and sophisticated immunologic techniques, now make it possible to approach the question of human retroviruses with vigor. These studies will focus on molecular cloning of the genome of "type-C virions" found in human placenta and tumor tissue, and identification and characterization of the protein and nucleic acid components of the "type-C virions."

Recent studies of the human papillomaviruses (HPV) have suggested that these viruses have a pathogenic role in the development of certain human carcinomas, particularly those of the anogenital tract. In addition, these viruses have long been associated with a broad spectrum of wart diseases. HPV DNA has been consistently detected in an unusual wart disease known as epidermodysplasia verruciformis which frequently converts to carcinoma. It has been reported that HPV is present in several types of anogenital tumors such as cervical and vaginal carcinoma *in situ*, and verrucous carcinoma. Another important observation which has further implicated HPV as the etiologic agent for cervical neoplasia was the detection of HPV DNA sequences in lymph nodes containing metastases. Lymph nodes which contained metastases were positive for exactly the same HPV DNA sequences present in the primary cancer. This result clearly showed that HPV genes are associated with cancer cells and that the sequences are maintained in those cells for the several generations required to form a metastatic lesion. Thus, the HPV genes appear to be necessary in order to maintain the malignant state. Upcoming studies in this area will focus on the possible clinical progression of HPV infections to dysplasia and carcinoma in human subjects and to relate this progression to the molecular biology of HPV. Attempts will be made to elucidate mechanisms of viral infection, replication and oncogenic transformation; the nature of the host's response to HPV; and the co-presence and possible involvement of other viral agents (such as herpes simplex and cytomegalovirus) with HPV in the oncogenic process.

Research in the area of human polyomaviruses will be continued. These human viruses provide unique opportunities to directly study the mechanisms involved in viral transformation of human cells. Activities will include determining the incidence and structure of polyomavirus DNA in normal and malignant human tissues; functional analysis of polyomavirus DNA isolated from human tumors with regard to the expression of viral genes, transformation activity in transfection assays, and maintenance of viral sequences when tumor cells are serially cultured; isolation and characterization of human lymphotropic virus and other new human polyomaviruses; and studies of the mechanism of persistent polyomavirus infections in man and the target cells involved in this interaction.

Epidemiology - A 1987 estimate of $50,270,000.

Continued emphasis will be given to case-control and cohort studies aimed at evaluating key hypotheses in cancer etiology. Case-control studies of selected cancers will be undertaken when high-risk communities are identified on the cancer maps or when major testable hypothesis and special resources become available. Whenever possible, laboratory procedures are incorporated into the epidemiologic studies to better clarify exposures, preclinical responses and mechanisms of carcinogenesis. Geographic monitoring of changes in cancer incidence and mortality will also be carried out to assess the impact of cancer prevention efforts. Initiatives will include expansion of the program to identify occupational carcinogens and new studies of general environmental exposures from air and water pollution. Detailed studies of the relationship between diet and cancer will be carried out, and an ongoing study exploring the reasons for marked differences between blacks and whites with regard to several types of cancers will be continued. Studies of radiation carcinogenesis will be expanded in an effort to quantify exposure and to correlate laboratory findings with the human experience. Particular emphasis will be placed on studies of individuals chronically exposed to low level radiation (e.g., individuals exposed to radon gas in the home or nuclear power workers) in an effort to develop models for understanding the action of carcinogens on human populations.

Epidemiologic studies are utilizing relevant environmental measurements in the general environment. The hypothesis that arsenical air pollution is in part related to lung cancer is being tested in one case-control study; in other case-control studies the risk of indoor air pollution is being evaluated in conjunction with measurement of radon daughter products, and in China where coal-burning stoves generate high levels of polycyclic hydrocarbons.

The risk from halogenated hydrocarbons in the water supply was evaluated by using a national case-control study of bladder cancer. Despite previous findings of an association based on geographic correlation studies, no overall relationship was found between drinking water quality and the risk of bladder cancer after making appropriate adjustments. However, in certain areas, a positive association was detected between bladder cancer risk and duration of exposure to surface (chlorinated) water, suggesting the possible role of agricultural chemicals. Further case-control studies are planned to clarify the effect of water pollutants on the risk of bladder, colon, and other cancers, with particular attention to agricultural areas.

Cigarette smoking is known to account for a substantial proportion of human cancer, and its effects on lung cancer risk were evaluated in a large-scale case-control study in several European cities. The size of this study made it possible to clarify the modification of risk due to changing smoking habits. It was found that cessation of smoking lowers lung cancer risk, but the reduction was proportionally greater for short-term versus long-term smokers. Little excess risk was seen among the group of persons who smoked for less than 20 years and then quit for 10 more years. Hence, the effect of smoking on lung cancer risk appears largely reversible if the habit is stopped soon enough. In addition, the risk for life-long filter smokers was about one-half that seen for life-long non-filter smokers. However, the risk for those who quit smoking for 10 or more years was much lower, being 20 to 30 percent of the risk seen among those who continued smoking. An understanding of the impact of tobacco use on cancer incidence continues to increase as new information about the causes of particular tumors comes to light. Recently completed case-control studies of renal cell cancer, renal pelvis cancer, nasal cancer, and cervical cancer indicate etiologic relationships to cigarette smoking, so that the list of cancers associated with tobacco products continues to grow and the need for preventive action is more urgent than ever.

Two recent studies in which NCI investigators participated have strengthened the evidence for the association of passive smoking with lung cancer risk. Each of these studies was a case-control study; one was in Japan and the other in the United States. Each study revealed that the risk of lung cancer tended to increase with the amount smoked by the husband, with the excess reaching two-fold or higher among non-smoking women whose husbands were heavy smokers. In neither of these studies could confounding factors (such as radiation or exposure to occupational carcinogens) be found to account for the association with passive smoking. The results of these two investigations are consistent with other reports and support the hypothesis of a possible association between passive smoking exposures and lung cancer. While the total evidence is not definitive, the results are suggestive enough to warrant further evaluation in larger studies where passive smoking exposures can be more fully quantified.

The use of smokeless tobacco has been linked to high rates of oral cancer, particularly among women in the southern United States. Efforts will be intensified during the coming year to clarify the cancer risks associated with snuff dipping and chewing tobacco, particularly since the use of such materials appears to be on the increase among young people in the U.S.

Studies aimed at clarifying the cancer risks from using various hormonal preparations, immunosuppressive drugs and selected chemotherapeutic agents will be continued. As an outgrowth of field studies in high-risk areas, a case-control study of kidney cancer was undertaken. An increased risk was associated with smoking, high relative weight, and analgesic drug use. Cigarette smoking was shown conclusively to be a significant risk factor for renal cancer, although its effect varied markedly by cell type. For renal cell cancer (mostly adenocarcinoma) heavy smokers experienced about a two-fold increase in cancer risk compared to non-smokers; for renal pelvis cancers (mostly transitional cell carcinoma), the excess exceeded ten-fold among both men and women, ranking this tumor as one of the cancers most strongly associated with smoking. Among women, high body mass index (weight/height squared) was clearly linked in a dose-response fashion to increased risk of renal cell cancer. Cancer risk increased nearly linearly with body mass, with women in the upper five percent of weight-for-height at almost six times the risk of renal cell cancer as women in the lowest quartile of this body size index. The association was primarily linked to weight gain in adulthood, since only a weak association was detected with weight at age 20. Finally, long-term (three years or more) regular use of analgesic drugs containing phenacetin was associated with a two-fold increase of renal cell cancer. For renal pelvis cancer, a four-fold excess was observed and was associated with long-term regular use of analgesics containing phenacetin or acetaminophen. Separate effects of phenacetin versus acetaminophen could not be disentangled. A new investigation of renal pelvis cancer will be launched to investigate this issue, since acetaminophen is now the leading analgesic used in the United States and since it is pharmacologically similar to phenacetin, a recognized human carcinogen. The role of hormones, antimetabolites and other medications in the development of cancer in women originally treated for benign hydatidiform mole (an abnormal pregnancy in which the membrane components of non-viable egg proliferate to form a grape-like structure) will also be evaluated.

Studies of HTLV-I based in several geographic hot spots for this retrovirus have further defined the importance of this virus as a human leukemogen. In Jamaica over 50 percent of all adult lymphomas are directly linked to HTLV-I, and molecular epidemiologic approaches have confirmed the monoclonal integration of the virus in the tumor tissue. In addition to the marked excess of T-cell malignancies associated with HTLV-I, there is also an apparent excess of HTLV-I associated with B-cell leukemias. Studies of the virus in normal populations suggest that HTLV-I acts as a leukemogen with a very long latent period. In addition, the very high rate of sero-positivity in migrant groups from an HTLV-I endemic area of Japan to Hawaii suggests that household transmission is a major source of exposure. Further, ongoing sero-conversion among migrants removed from the viral endemic environment suggests the possibility that a sero-negative, virus-positive latent infection with the virus may be important with potential implications for the leukemogenic process. Efforts to investigate further the transmission of HTLV-I in migrant populations and its relationship to acute T-cell leukemia will focus on environmental and lifestyle factors and should provide a better understanding of the modes and determinants of viral infection.

Major insights concerning the role of HTLV-III in the AIDS epidemic have emerged from epidemiologic studies during the past year. Longitudinal studies have defined the natural history of the virus infection including risk factors for transmission and the recognition of a virus-positive, antibody-negative state which may antedate the subsequent sero-conversion in some portion of study subjects. Recent analyses have quantified a risk approaching 30 to 40 percent in one cohort of virus-positive individuals for the subsequent development of AIDS. A progressive process of immunoablation has been directly linked to the duration of infection in prospectively followed cohorts. In addition, further studies of special risk groups will attempt to clarify the potential risk for acquiring HTLV-III infection through occupational exposure in the hospital setting. Greatly expanded studies on HTLV-III and AIDS will also be carried out in spouses of hemophiliacs, spouses of drug abusers, and in pregnant AIDS patients and HTLV-III positive women, and in their offspring.

A major focus of activities has been to define the extent of AIDS in some areas of Africa and the relationship of recognized retroviruses to each other and to putative new retroviruses that may be recognized in time through current epidemiologic investigations. These studies have defined the broad occurrence of sero-reactivity to all three known retroviruses (HTLV-I, II and III) in equatorial Africa, and raise the possibility that the reactivity represents possible cross-reactivity with yet-to-be defined retroviruses. In addition, true HTLV-I infection has been confirmed, and adult T-cell leukemia recognized in Africa. The epidemiology of HTLV-III in Africa has confirmed that there is an epidemic of AIDS in certain countries in Africa, where studies are attempting to clarify the modes of transmission of the disease through heterosexual contact.

A number of important observations as to the relationship between exposure to ionizing radiation and development of cancer have emerged recently. A new survey of breast cancer among atomic bomb survivors revealed for the first time a dose-related excess risk among women exposed under age 10, indicating that the immature breast may be especially susceptible to the carcinogenic effects of ionizing radiation. A study of childhood cancer in twins indicated a two-fold excess risk associated with prenatal x-ray, suggesting that the association with leukemia and other cancers is due to radiation rather than the indications for pelvimetry. In a large-scale international survey of cervical cancer, radiotherapy was found to be associated with a small, but significant, increased risk of leukemia. This appears to be related to the comparatively low doses of radiation absorbed by bone marrow outside the pelvis, since pelvic marrow is probably sterilized by the large therapeutic exposures. Studies in this area will continue to investigate the relationship between cancer risk and ionizing radiation, especially exposure to high doses, and efforts will be made to improve estimates of risks associated with lower doses. An immediate practical need is for risk estimates on which to base regulatory and other decisions about the use of nuclear and radiological technology in medicine and industry, and to assess the value of exposure avoidance as a means of cancer prevention.

In assessing many risk factors, greater efforts will be made to incorporate biochemical and molecular probes of exposure, response, and mechanisms of action. Studies of cancer-prone families provide exceptional opportunities to apply new molecular techniques, including those indicating the presence of human oncogenes. The AIDS epidemic and the study of T-cell leukemia will continue to receive emphasis by linking epidemiology with immunologic and virologic probes, especially those related to the retroviruses, HTLV-I and HTLV-III. The relation of human papillomaviruses to cervical and other cancers will also be emphasized. Although traditional methods of epidemiology have succeeded over the years in identifying and characterizing many risk factors for cancer, the task ahead appears more formidable as etiologic hypotheses become increasingly specific. With recent advances in the development of usable experimental probes, it is likely that biochemical and molecular epidemiology represents a strategy to deal with and, hopefully, settle many key issues in cancer etiology.

More attention will be given to the study of less common neoplasms, involving collaborative case-control studies in several areas or centers, often utilizing the network of SEER registries. Special efforts will be made to ensure that data from epidemiologic studies are utilized for critical evaluation of methodology and development of more efficient approaches, investigation of carcinogenic mechanisms of action, and research into quantitative risk assessment.

Nutrition - A 1987 estimate of $23,000,000.

An increasing body of scientific evidence supports the hypothesis that diet is an important determinant of cancer risk. General dietary patterns, nutritional status, specific foods and food groups, and food additives are all recognized as possible factors for cancer. Efforts are now underway to test and quantify in human populations those hypotheses about the role of diet in carcinogenesis that have resulted from animal studies, in vitro experiments, and epidemiologic observations. Nutritional epidemiology can reveal broad correlations between dietary patterns and cancer, which then serve as the basis for further laboratory and epidemiologic research and clinical trials. Certain factors in the diet may initiate carcinogenesis, others seem to promote it, while still others seem able to reduce cancer risk. A major research effort is underway to learn more about how specific components of the diet either increase or decrease the risk of cancer. Research in chemoprevention involves identifying and characterizing agents with preventive activity, detailed study of efficacy and toxicology to select the most promising agents, and clinical trials to test those with the most potential in humans.

A number of micro- and macronutrient inhibition clinical trials are currently in progress. These can be classified on a site-oriented basis. First, several studies have as their purview all anatomic sites. One of the first chemoprevention trials to be initiated is a study involving U.S. physicians and is testing the preventive potential of beta carotene. The second study, which is now site specific, is currently in a pilot phase in the U.S. where dentists are evaluating retinyl palmitate, sodium selenite, and the vitamins B_6 and E. Six studies focus on prevention of lung cancer and the populations include individuals with dysplastic sputum cytology (one study), smoking history (three studies), or asbestos exposure (three studies). The agents that are proposed or have been initiated in these studies include folic acid/vitamin B_{12}, retinol, 13-cis retinoic acid, beta carotene, and vitamin E. Six studies in prevention of skin cancer are being conducted. Risk factors include the presence of previous skin cancers, a precancerous condition (actinic keratosis), or a specific population group which is at high risk for skin cancer, namely Albinos in equatorial Africa. The spectrum of agents being evaluated in these studies includes beta carotene, vitamins C and E, retinol, and 13-cis retinoic acid. There are five studies focusing on prevention of colon cancer. The selection factors are either familial polyposis or adenomatous polyps. The agents being studied include beta carotene, vitamins C and E, and 13-cis retinoic acid. One study combines chemoprevention and modification of diet. One group in this study is receiving bran as part of the intervention. In cancer of the cervix, another study involves topical application of retinoids and another study involves systemic administration of folic acid. Participants are selected on the basis of dysplasia on a Pap smear.

Chemoprevention trials involving intermediate endpoints will be implemented. The major objective will be to encourage cancer chemoprevention clinical trials which utilize biochemical and biological markers to identify populations at risk and/or to provide intermediate endpoints that may predict later reduction in cancer incidence rates.

A population-based, case-control study of lung cancer in areas with elevated rates for that tumor in the white male population is in progress. A component of the study assesses whether carotene, retinol, total vitamin A, or the broader related food groups (or a non-nutritional component) are associated with reduced risk. Another population-based case-control study of lung cancer was initiated among black men and white women in high incidence areas. The relative risks for these populations and the ability of poor diet to explain the rapid rise in lung cancer among U.S. blacks will be evaluated. The dietary component of the interview, expanded to assess other nutrients possibly correlated with retinol and/or carotene intake, like vitamin C, includes the usual adult frequency of consumption of 59 food items and a history of vitamin pill usage.

A case-control study of colorectal cancer is being carried out in three regions of Florida with high rates of immigration from the Northeast and North Central states. The U.S. cancer maps had shown that colorectal cancer mortality rates for white men and women are lower in the South by about 50 percent than in the Northeast or North Central states, a reduction that could not be explained by differences in income or population density. Close examination of the age-specific cancer mortality rates for those counties in Florida where many northerners move at retirement revealed that colorectal cancer rates in those counties were as low as in southern counties of comparable population and did not rise toward the northern rates at older ages. This study seeks to explore the characteristics of this apparent reduction in risk, quantify it, and to see whether it might be due to some change in lifestyle (e.g., eating more fruit and vegetables or drinking different water), or whether it might be due to some selected healthy subset of northerners.

A population-based, case-control study of breast cancer in young Oriental-American women was started recently. When Oriental women migrate to the United

States, their low rates of breast cancer rise toward American rates over a period of several generations as they adopt a more westernized diet. In this study population, diet should be sufficiently heterogenous to permit the identification of the strong associations of diet with breast cancer risk that are assumed to exist. The study subjects will be 55 years or younger so that many of their mothers, as well as they, can be interviewed about their childhood and adolescent diets. The hypothesis that diet is operative on breast cancer risk primarily during these two periods of the life span can be evaluated. This study will also permit evaluation in Oriental-Americans of the standard breast cancer risk factors and an estimation of the difference in Oriental and Caucasian breast cancer rates attributable to various risk factors. Serum will be collected from the cases and the controls for cholesterol, triglyceride, lipoprotein, tocopheraol, retinol, carotene, and selenium determinations. In order to study the interrelationships of ethnicity, dietary patterns, hormonal levels and disease, urine and serum will be collected for hormonal assays.

A study is being designed to measure specific fecal mutagens and total Ames test mutagenicity in several populations at high risk of colon cancer and in matched healthy controls. The high-risk groups will be: 1) people with a strong genetic predisposition to colon cancer (familial polyposis, Gardner's syndrome, and certain families with an autosomal dominant risk); 2) colon cancer patients who needed only limited surgery and have recovered; and 3) people suspected of having colon cancer who have not yet undergone any diagnostic tests. The third group will offer the opportunity to monitor fecal mutagenicity, serum nutrient levels, and possibly other biochemical measures through the phases of diagnosis, hospitalization, surgery, perhaps chemotherapy and/or radiation, and gradual recovery.

To test dietary, occupational lifestyle, dental, and other hypotheses regarding risks for oral and pharynx cancer, a case-control study has been initiated. Information on dietary patterns will include an extensive food frequency checklist (usual adult frequency), food preparation, special diets, vitamin supplements, height and weight, and alcohol intake. Dietary indices to be formed from the data include retinol, carotene, nitrites, and specific food groups (e.g., fruits and vegetables).

A large, multi-center case-control study of pancreatic, esophageal, prostate cancer and multiple myeloma among blacks and whites of both sexes is being developed. All of these cancers are more common among blacks than whites. Sufficient numbers of black cases will be studied to evaluate how the relative risks and exposure levels differ between the races for these cancers. Aspects of diet that will be assessed by interview include nutrient deficiency (esophageal cancer), patterns of fat consumption (pancreatic and prostate cancer), and coffee and methylxanthine intake (pancreatic cancer). Blood will be collected in order to measure selected micronutrients, lipids, and hormones in the plasma.

In 1982 to 1984 the Environmental Epidemiology Branch (EEB), in cooperation with the National Institute of Aging, other NIH Institutes, and the National Center for Health Statistics, traced and reinterviewed, if still living, the 14,000 adults examined 8 to 14 years earlier in HANES I (the U.S. Health and

Nutrition Examination Survey). By collecting intervening cancer morbidity and mortality data for this cohort, associations between dietary patterns prior to disease and the common cancers can be evaluated. As these people were traced, their social security numbers were obtained so that further cancer mortality could be monitored with the National Death Index. A comprehensive dietary section, designed to assess exposure to those food groups, food items, nutrients, additives, and cooking practices now suspected of being related to cancer, was drafted by the EEB and incorporated into the reinterview. Analysis of these new data should provide useful descriptive information on dietary practices and dietary variations within the United States. In addition, the expanded dietary section should facilitate future analyses of diet and cancer relationships within this cohort.

The feasibility phase of a trial of a low-fat diet in women at increased risk for breast cancer has begun in three clinical units, one nutritional unit, and one statistical unit, and workshops for protocol development have been held. Data from this phase of the study will be analyzed and reviewed to determine if a full-scale trial should be performed.

An International Food Composition Data System is being developed. This international food composition system will enhance the quality, quantity, and accessibility of nutrient and non-nutrient data. This comprehensive data system will provide needed information for formulation of public policy on diet-related public health issues. Studies on dietary fiber and the components of fiber in foods are being conducted to develop adequate methodology for detection and quantitation of these components in foods. The physiochemical effects of dietary fiber in humans is being studied to investigate the metabolic and physiologic functions of dietary fiber and to elucidate their possible protective role in carcinogenesis. Studies to develop and implement methods and strategies for dietary behavior modification for risk reduction are being initiated. The specific objective will be reduction of dietary fat and increase of dietary fiber.

Two Clinical Research Nutrition Units have been established to create or strengthen foci in biomedical research institutions for multi-disciplinary research in clinical nutrition in order to develop new knowledge about specific nutrients in health throughout the life cycle, and in the prevention and treatment of disease; to strengthen training environments in order to improve the education of medical students, house staff, practicing physicians, and allied health personnel in clinical nutrition; and to enhance patient care and promote good health by focusing attention on clinical nutrition and generating nutritional information for the public.

The NCI's Office of Cancer Communications operates the Cancer Prevention Awareness Program, which provides messages to the public that changes in dietary habits (e.g., increasing fiber, reducing fat intake) can reduce an individual's risk of cancer. In 1985 the Cancer Prevention Awareness Program began developing plans for a Nutrition Education Program including collaborative projects with the American Cancer Society, the development and distribution of nutrition information for the public, and cooperative arrangements with other internal and external public and private organizations involved with improved nutrition.

Detection and Diagnosis Research

Purpose and Method of Operation

Research on detection and diagnosis is directed toward improving the ability; 1) to identify populations and individuals at high risk; 2) to detect cancer at earlier stages and to detect precancerous abnormalities; 3) to characterize different tumor types, determine the stage of development and the prognosis; and 4) to monitor more effectively the changes during and following therapy. Identification of populations at high risk will result in appropriately targeted and more effective screening programs; development of new and better tests for detection will result in the ability to detect tumors before they become invasive or metastatic. Better classification schemes will provide more information concerning diagnosis and prognosis. Improvements in detection and diagnosis are critical to the physician's choice of the most effective therapeutic approach to decrease mortality from cancer and to improve survival rates.

The emphasis in detection and diagnosis related research is on the transfer of conceptual and technological developments from basic research to the clinic. Following small scale feasibility studies, systematic evaluation of the most promising discoveries is carried out in major research clinics and Cancer Centers in large-scale population studies.

There has been an increase in the quality and diversity of diagnostic research in the past few years. Various program initiatives aimed at encouraging research in specific areas of cancer diagnosis have been responsible for some of the increase. But there is also greater recognition within the scientific community that technologies and information emerging from basic research programs such as Tumor Biology, Immunology and Biological Carcinogenesis can now be effectively exploited for development of clinical applications.

Detection and diagnosis research can be divided into five major areas: genetic studies, radiologic and non-radiologic imaging, immunologic approaches, biochemistry and pathology/cytology. The rapid progress in applying new genetic technologies to cancer diagnosis is expected to continue to provide more powerful diagnostic tools and to aid in the identification of individuals at high risk for particular cancers. New diagnostic imaging techniques are improving the ability to detect small lesions and to provide better staging information. Production of new monoclonal antibodies is now routine and this has fueled an explosion of research to identify new tumor markers and to reevaluate the usefulness of known tumor antigens. Basic biochemical studies of tumor cells have provided new ideas for detecting particular cancers by identifying metabolic byproducts found in biological fluids. All of these approaches and technologies have had an impact on the basic tools of cancer diagnosis: pathology and cytology. The developments in cancer diagnosis research promise to improve significantly the clinician's ability to identify cancer at an earlier stage and to treat it more effectively.

Rationale for the Budget Request

The 1987 budget estimate of $78,172,000 represents an increase of $529,000 from the 1986 estimate. The program plans for 1986, along with expected accomplishments, are as follows:

Epidemiology - A 1987 estimate of $13,708,000.

The Surveillance, Epidemiology, and End Results (SEER) program, begun in 1973, has now been in operation for sufficient time to allow consistent estimates of cancer patient survival changes. The vast potential of the SEER program is just now beginning to be realized as the data collected over the past decade have begun to mature. Studies of differences in incidence and survival among populations are valuable in directing the NCI cancer control programs and providing new research leads. Monitoring trends in cancer incidence and survival continues to be important to the NCI's programs.

New opportunities in cancer surveillance are emerging. An increasing trend among the states is the development of cancer registries, which generally monitor incidence rates in defined populations or in large parts of states. The opportunity for the NCI to play a coordinating role in the development of these databases is an important one. The development of additional technical assistance and guidance may yield the further opportunity to utilize these data to augment the SEER program in its challenge of monitoring cancer in the U.S. population.

Another fresh development is increasing the NCI's ability to look at cancer risk factors and health behaviors which affect cancer risk. In the past, the NCI had to rely on infrequent surveys conducted by contractors or by the private sector. In calendar year 1987, the NCI will join with the National Center for Health Statistics in its annual National Health Interview Survey (HIS). The NCI cancer control supplement to the HIS will allow for the collection of information in 52,000 households on cancer risk factors; cancer screening behaviors; and knowledge, attitudes, and behaviors related to the control of cancer. This survey will be the beginning of standardized methods to monitor the nation's progress toward accomplishing intermediate mortality reduction objectives set by the NCI.

Diagnostic Research - A 1987 estimate of $63,476,000.

The application of molecular genetic technologies to cancer diagnosis appears to be most promising. Breakthroughs in basic tumor biology that have demonstrated that genetic alterations are involved in tumorigenesis will be exploited clinically. Differences in the levels of the product of the *ras* oncogene, $p21^{ras}$, have been correlated with various stages of colon cancer; this provides prognostic information by indicating the state of differentiation of primary and metastatic colon cancer tissue. The presence of an altered protein product of another oncogene, c-*abl*, is being evaluated as a prognostic indicator in patients with chronic myelogenous leukemia. Amplification (presence of extra copies of a gene) of the N-*myc* oncogene is associated with advanced stage of human neuroblastoma; the usefulness of this correlation in determining therapeutic regimens and prognosis will be further evaluated.

These and other genetic approaches to cancer detection and diagnosis will continue to be encouraged.

Another molecular genetic technique that is being exploited for diagnosis involves the use of restriction fragment length polymorphisms (RFLP). This technology is based on the identification of changes in the pattern of bands revealed when cellular DNA is cut with particular restriction enzymes. The fortuitous finding of a polymorphism associated with Huntington's disease has encouraged researchers to look for RFLPs that can identify individuals at risk for other diseases, including cancer. The met oncogene, found in a region associated with non-random chromosomal alterations in some patients with acute non-lymphocytic leukemia, has proven to be a useful marker in the search for the cystic fibrosis gene. Investigators are screening DNA from patients with multiple endocrine neoplasia, type II, to find a RFLP that might be useful in identifying members of families who might be at greater risk of developing this disease. DNA from families with unusually high incidences of cancer is also being screened for polymorphisms that might be useful for diagnosis or prognosis. Although this new approach may prove to be important, any definitive results will accumulate slowly because of the extensive trial and error screening required for each type of cancer.

Sophisticated techniques for examining chromosomal alterations have been used to demonstrate that specific chromosomal abnormalities are present in a number of hematopoietic malignancies and that these observed changes are of diagnostic value. Similar studies in solid tumors have been hampered by technological difficulties. Advances in the ability to culture some solid tumors, e.g., gynecologic tumors, have provided the means by which important genetic and biochemical data may be obtained for these tumors. Research to overcome technical problems and to determine the value of cytogenetic observations in these tumors will be actively encouraged through program initiatives.

One problem that has increasingly plagued both basic research on the biology of human solid tumors and associated research on diagnostic approaches has been the difficulty of obtaining sufficient tumor tissue. A large amount of valuable tissue is routinely discarded because of difficulties in establishing coordination between the research laboratories and the surgeons and pathologists. To overcome these problems and to facilitate access to the requisite tumor tissue, the NCI will establish a nationwide cancer tissue procurement network.

The correlation between heritable cytogenetic anomalies and predisposition to cancer will be examined in depth in small-scale family studies. This research should result in improved ability to identify individuals at greater risk for particular cancers.

New and easier methods for production of monoclonal antibodies will be exploited to elicit potentially useful diagnostic reagents. These reagents will be used in the continuing search for more specific tumor markers, particularly those present in body fluids which would permit detection by non-invasive procedures. Promising markers include the peptides that are released by certain lung tumors and perhaps by other tumors of neural origin. Certain urinary factors also look promising for the detection of cancers of the bladder and kidney.

Monoclonal antibodies are particularly useful in pathological diagnosis because their specificity permits more refined classification schemes. Specific monoclonal antibodies developed to detect cytoskeletal proteins (components of the subcellular filamentous network) can be used to identify the cell of origin of specific neoplasms. Considerable research will be devoted to production of new reagents and improvements in the sensitivity of detection. Efforts will also continue to develop better assays for hormone receptors which are of particular importance in diagnosis and prognosis of cancers of the breast and reproductive organs. Advances in nuclear medicine and diagnostic imaging are also dependent on monoclonal antibody technology. Research efforts will continue to develop effective methods to produce monoclonal antibodies of human origin for use in diagnostic imaging. Human monoclonal antibodies are necessary to prevent immune reactions on repeated administration and are also expected to provide improved sensitivity and specificity. These reagents will be useful in both diagnosis and therapy.

Research directed toward the development of current imaging technologies such as positron emission tomography (PET) and ultrasound imaging will continue. Improvements in anatomical imaging techniques are expected to enhance the ability to visualize and identify primary and metastatic lesions and to monitor the spread of disease. Single photon emission computed tomography (SPECT) is a technique which, unlike PET, utilizes conventional radionuclides. Continued support in this area will lead to the development of less expensive approaches to three dimensional imaging. One necessary focus of this research is the identification of radionuclides suitable for use as diagnostic radiopharmaceuticals with these systems. Magnetic resonance imaging (MRI), a technique which does not utilize ionizing radiation, is being used increasingly. It has particular value in delineating tumors that are invading adjacent tissues or organs. Research on this new technology will continue in order to increase its usefulness in identifying small tumors and in staging. Investigators have now used sodium and phosphorous imaging techniques in MRI research to distinguish malignant from benign tumors solely on their imaging characteristics. This represents a major breakthrough which may eventually allow specific tissue diagnosis without need for surgical biopsy.

New technologies are rapidly being incorporated into practical systems for automated microscopy. Advanced computer systems, digital laser disc technology, and expert systems (computer programs which mimic the analytical process of experts) will lead to fully automated morphological analysis systems with important implications in diagnosis, prognosis and monitoring of therapy. The developments will substantially decrease the time required for each analysis and thus improve the efficiency and utility of automated systems.

Flow cytometry, a technique for rapid analysis of cellular characteristics, is becoming an important tool in both basic research and clinical practice. The development of techniques for the detection of specific cellular components using monoclonal antibodies labeled with fluorescent dyes is being emphasized. Techniques are being developed that allow simultaneous detection of several different markers and separation of specific cell populations of interest.

Flow cytometry is also being used to analyze genetic characteristics at both the chromosomal and the molecular levels. Techniques for rapid separation and sorting of chromosomes have been developed and are being improved. These techniques combined with genetic probe technology promise to provide an important and rapid methodology for identifying individual chromosomes, and producing genetic maps. Resulting data will simplify evaluation of genetic alterations related to tumorigenesis and will have applications to both diagnosis and prognosis.

One of the major dilemmas in cancer diagnosis is determining which tumors will be aggressive and which will be indolent. Morphological classification systems often have been unable to provide this type of information. Efforts will be supported to apply new diagnostic approaches to the development of more informative criteria and classification schemes. Considerable research is underway to determine whether immunophenotyping of lymphomas will provide better diagnostic and prognostic information. Genetic technologies will also be applied to delineating which lymphomas and leukemias will be more responsive to therapy.

The NCI will facilitate the transfer of basic research developments into clinical diagnostic applications through a novel program initiative. Investigators who are already supported by the NCI will be encouraged to capitalize on developments with clear diagnostic implications and importance by allowing them to apply for supplementary support that will enable them to test the feasibility of new assays.

Theoretical work is underway concerning unresolved problems in the design and analysis of cancer screening programs. This work will increase our understanding of the possible role of screening in reducing death rates for some forms of cancer, and possibly help in finding less costly means of assessing screening programs.

Emphasis will continue to be placed on improving approaches to early detection, diagnosis and prognostic indicators. In the area of bladder cancer, the clinical importance of tumor heterogeneity will be explored relative to prognostic markers, tumor resistance and tumor recurrence after initial treatment. Other areas with implications for bladder diagnosis and prognosis relate to chromosomes in solid tumors and continuing emphasis on cytometry and markers. Flow cytometry is now developed sufficiently to be considered for trial as an outpatient laboratory test for urinary bladder detection, diagnosis and classification. Data from the bladder cancer screening program of the DuPont Company are being analyzed to assess the relationship of urinary cytology and blood tests to exposure and to the development of cancer, to evaluate the sensitivity and specificity of the screening tests, and to determine whether or not screening improves survival of bladder cancer cases.

Tumor markers and their significance in the management of breast cancer continues to be an area of emphasis. Specific markers will be evaluated for potential use in monitoring the clinical status of breast cancer patients and in developing new strategies for treatment. One important aspect is the need for testing and standardization of antibodies that are currently available. Histopathology of "benign" breast lesions and their potential for progressing to malignancy will receive attention with emphasis on quantitative risk assessment. This is complemented by studies on morphological characteristics of the normal human breast in conjunction with longitudinal mammographic evaluation with aging. In addition, the potential for breast fluid analysis in breast diseases will be explored.

A major problem in the area of prostate cancer continues to center around the factors that control progression from latent to clinical carcinoma. Mechanisms and patterns of prostate metastasis will be explored, as will prognostic factors for malignancy. This has broad implications for therapy, particularly for identifying individuals who might be candidates for particular therapies. A related area to receive attention is the quantitative assessment of tumor burden, invasiveness and responsiveness. This has clinical implications for diagnosis and for early detection.

An ongoing randomized controlled trial to determine whether screening for occult blood in the stool will decrease mortality from colon cancer will continue. This is the only trial of its kind in this country and the exceptionally high rate of the participant compliance is expected to provide statistically significant results. Current assays for occult blood are not sensitive and specific enough to identify all individuals with blood in the stool without also registering significant numbers of false positives. Research will continue to develop better tests which can be made available if screening for occult stool blood proves effective. The progression of colonic polyps to malignancy will continue to receive attention. Markers of premalignancy and their inheritance will be explored as a potentially exploitable model of human colon cancer progression. Related to this is the exploration of prognostic factors on colon cancer with development of markers and experimental models.

Immunology - A 1987 estimate of $988,000.

Efforts to isolate, identify, purify, and characterize tumor-associated antigens relating to large bowel cancer will continue.

Research designed to improve the assessment of the various types of white blood cells infiltrating breast cancer will continue, in order to determine their value as prognostic indicators.

Treatment Research

Purpose and Method of Operation

The past 30 years have witnessed a significant improvement in the effectiveness of treatments available to patients with cancer. The introduction of chemotherapy and its successful use in leukemia, lymphoma, and other solid tumors in the past two decades has now been followed by the identification of an entirely new form of therapy, the use of adoptive immunotherapy with white blood cells conditioned with the immune stimulant, Interleukin-2. In 1985, Dr. Steven Rosenberg of the NCI reported the first successful use of adoptive immunotherapy in patients with drug-resistant tumors of the colon, kidney, and lung, and malignant melanoma. This discovery represents a milestone in the NCI effort to develop effective biological treatments for cancer. To place this and other important developments in context, it is useful to review briefly the progress in treatment of patients with advanced forms of cancer over the past three decades.

While the principles for curative surgery for patients with localized tumors had been firmly established during the first half of this century, in 1950 there existed no effective treatment for the two-thirds of cancer patients whose disease had spread to distant sites at the time of diagnosis. The introduction of high-energy radiotherapy in the mid-1950s further improved the cure rate for patients with localized tumors of the head and neck, lymph nodes, and reproductive organs, and in many cases provided an effective and less debilitating alternative to surgery, but the problem of treating far-advanced disease, as found in the majority of patients with cancer of the breast, lung, and colon, as well as leukemia and lymphomas (lymph node tumors), remained unresolved. At this time, in 1955, researchers at the National Cancer Institute described the first cure of advanced cancer with drugs, the treatment of metastatic choriocarcinoma (a tumor that arises during pregnancy) with the folic acid antagonist, methotrexate. It was thus shown that, as in the treatment of infection, drugs could also be used to selectively eliminate tumor cells from the body without serious toxicity to the host.

In response, Congress established a program to develop new drugs for the treatment of metastatic malignancy. That program consisted of two arms, a preclinical component designed to discover and develop new agents from among the many synthetic and naturally-occurring chemicals available in industry and academia, and secondly a clinical trials component designed to test the best of these candidate drugs in man and to identify their activity against specific types of human cancer. The preclinical discovery efforts screened new compounds against rapidly proliferating leukemias in mice; the use of these murine tumors was based on the guiding concept that the most effective way to treat cancer was to block its ability to proliferate or grow. In addition to these screening efforts, chemists designed a series of compounds with blocked specific steps in the synthesis of the genetic material, DNA. Together, these drug discovery and testing efforts proved remarkably successful in finding 40 new drugs, such as vincristine, L-asparaginase, adriamycin, and cyclophosphamide, which had potent activity against the more rapidly growing tumors of childhood and early adult life. These drugs, when used with appropriate intensity and in specific sequence and combinations, were found to

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cure patients with childhood leukemia in the early 1960s and subsequently Hodgkin's disease, lymphoma, and advanced testicular cancer by the mid-1970s.

More recently, a major innovation in the use of chemotherapy was the concept of adjuvant chemotherapy. Because drugs are able to cause at least partial regression of advanced tumors in the majority of patients with breast cancer, it was reasoned that the use of drugs at an earlier point in the disease, when the number of tumor cells was smaller and the patient better able to accept full doses of treatment, would possibly cure patients who were not curable at more advanced stages of disease. In practice this meant that patients who had undergone primary surgery for breast cancer and who were established (by the presence of tumor in lymph nodes at the time of surgery) to have a high risk of recurrence at distant sites, received 6 to 12-month periods of treatment with chemotherapy. As concluded at an NIH consensus conference in September of 1985, adjuvant chemotherapy has produced at least a 25 percent reduction in the death rate of women below the age of 50 who have high-risk forms of breast cancer. Improvements in survival also result from hormonal therapy and chemotherapy in older women with high-risk forms of breast cancer. This concept of adjuvant cancer treatment has been successfully applied to decrease recurrence of many of the solid tumors of children, including osteosarcoma, rhabdomyosarcoma (a tumor of muscle), and Ewing's sarcoma and osteosarcoma (both tumors of bone origin). In studies completed this year, decreased recurrence rates were observed in high-risk adult patients with rectal cancer, colon cancer, and adenocarcinoma of the lung treated with chemotherapy in the adjuvant setting. Taken together, early (adjuvant) treatment of these diseases can be expected to save the lives of 22,000 Americans each year.

This progress in drug therapy of cancer was largely based on the concept that cancer cells could be controlled by compounds that block proliferation and, specifically, that interfere with the synthesis and function of the cancer cells' genetic material, DNA. In order to make significant inroads into the treatment of malignancies which respond poorly to current therapies, particularly the far-advanced tumors originating in the colon, lung, and breast, scientists at the National Cancer Institute and in NCI-supported research programs have turned their attention to two issues: 1) elucidation of the fundamental biochemical processes which lead to a lack of response or resistance to chemotherapy; and 2) the identification of new biological and immunological targets for drug development, in addition to the traditional target of inhibition of tumor cell proliferation. Major progress has been made in both efforts during the past year.

A meeting of leading experts took place at the National Cancer Institute in December of 1985 to consider progress in understanding tumor resistance to drug therapy. At this meeting, it became clear that a major step forward has been taken in understanding the fundamental processes that allow tumor cells to escape damage by an important class of antitumor drugs, the antibiotics derived from plants, fungi, and other natural sources. Specific cell surface proteins (the P170 glycoprotein) are developed by resistant cells to carry toxic drugs out of the cell; in addition intracellular proteins, such as the anionic glutathione transferase, are synthesized to inactivate these agents. Basic similarities have been discovered between the process that leads to tumor formation by carcinogens (carcinogenesis), and the process of drug resistance.

For example, the newly discovered enzyme which attaches phosphate groups to regulatory molecules on the cell surface, known as protein kinase C, is markedly increased in activity during both processes. This fundamental link between carcinogenesis and drug resistance may explain the unique ability of tumor cells to escape drug toxicity, and suggests an important new target for antitumor drug design, the protein kinase C and its related phosphoinositol cycle.

In addition to the progress in understanding the reasons for drug resistance, major advances have been made in 1985 in the development of entirely new approaches to cancer treatment. These approaches are based on the knowledge and tools of modern molecular biology, immunology, and genetics; these disciplines have provided new targets for cancer treatment. Progress in understanding the basic properties of the malignant cell has led to appreciation that the cancer cell is dependent on unique growth factors, has specific surface proteins, and can be recognized and destroyed by special types of cells, called "killer cells", found in the immune system. The specific chemical processes that allow the cancer cell to invade neighboring tissue and to spread to distant parts of the body have been clarified and, in turn, have suggested new therapeutic approaches. All of these biological properties have become the subject of the Biological Response Modifiers Program, the newest treatment research program of the NCI. This program, established in 1980, is now paying its first dividends in terms of the highly effective treatment of hairy-cell leukemia with alpha interferon, and the important demonstration this year that patients with advanced tumors of the colon and kidney and with malignant melanoma (a highly lethal form of skin cancer) respond to a new form of immunotherapy. This treatment, developed by Dr. Rosenberg, involves the generation of cytotoxic killer cells (lymphokine-activated killer cells, or LAK cells) by exposing the patient's normal white blood cells to the growth factor Interleukin-2. These activated lymphocytes are able to recognize and selectively destroy cancer cells. This new approach has produced 12 responses in 32 patients with solid tumors resistant to other treatments and holds substantial promise as a new approach to cancer treatment. Expanded trials of LAK therapy have been established in 10 centers nationwide under NCI sponsorship. Other types of biological therapy are also advancing to clinical trials.

A number of other new biological approaches reached the initial stage of clinical trial in 1985. The NCI, as well as several private industrial firms, initiated clinical trials with human tumor necrosis factor, a protein isolated from human white blood cells by recombinant DNA technology. Although tumor necrosis factor is highly toxic to cancer cells, it appears to have little effect on normal tissues.

The promise of monoclonal antibody therapy is being seen in early clinical trials. These antibodies, which recognize single specific surface proteins on malignant cells, proved capable of causing tumor regression in patients with malignant melanoma in new NCI-sponsored trials in 1985, and have been used successfully to remove tumor cells and donor immune cells from bone marrow in clinical bone marrow transplantation experiments. Progress has continued in arming these monoclonal antibodies with radioisotopes and potent toxins in an effort to target these toxic substances specifically toward tumor cells. These antibody-toxin conjugates entered clinical trial for the first time in 1985 and these studies will be expanded in 1986.

Thus, the promise of translation of basic biology advances into effective new treatment has been realized in the LAK studies and monoclonal antibody experiments undertaken during the past year in treatment research. Together with the clinical application of research findings in cancer prevention and improved cancer diagnosis, prospects are increasingly favorable for achieving the eradication of cancer.

Rationale for the Budget Request

The 1987 budget estimate of $365,128,000 represents a decrease of $205,000 from the 1986 estimate. The program plans, along with expected accomplishments, are as follows:

Preclinical Treatment Research - A 1987 estimate of $176,545,000.

During the early period of drug development, research focused on a single feature of the cancer cell - its ability to proliferate and grow in an uncontrolled fashion. The target molecule for these chemotherapeutic agents was DNA, the building block of genetic material within the cell. Other factors have recently been identified that control other features of the malignant process and represent additional targets for new treatment strategies.

Foremost among the obstacles to curing cancer with drugs is the ultimate outgrowth of resistant tumors that do not respond to treatment. The sequence of initial response, and then failure due to drug-resistant tumor, occurs commonly in breast cancer, adult leukemias, ovarian cancer, and childhood malignancies. Of particular interest was recognition of the fact that cancer cells selected for resistance in the presence of a single drug (usually of the natural product type) often express cross-resistance to seemingly unrelated natural products. During the past year, outstanding progress has been made in identifying the biochemical, molecular, and genetic changes responsible for multi-drug resistance, some of which have been described in the introduction to this section. One of these changes, the presence of a new membrane marker, the P170 glycoprotein, has been recently demonstrated in resistant tumor samples taken from patients with ovarian cancer following treatment. This marker protein, a product of gene amplification, allows resistant tumor cells to extrude (eliminate from the cell) cytotoxic drugs. Identification of this marker protein may now make it possible to predict resistance by biochemical analysis of human tumors and affords the possibility of selectively destroying resistant cells with monoclonal antibodies to the membrane marker.

However, it now has been learned that the P170 protein is only one of several changes which occur in tumor cells in response to anticancer drugs. For many years, cancer researchers have been puzzled why cancer cells, but not normal tissues, are able to become resistant to cytotoxic drugs. New findings in the past year suggest that the basic process of transformation to a malignant cell may bring with it the ability to mount effective defenses against toxic substances such as cancer drugs. For example, changes in human drug-resistant cells described during the past year include increased intracellular levels of the enzymes protein kinase C and glutathione transferase. These changes mimic those seen in early stages of malignant transformation, and indeed are believed to be essential steps in the process. Protein kinase C is activated by the potent tumor promoter compounds, the phorbol esters; of great interest is the finding that the phorbol esters also convert sensitive tumor cells to drug resistance. These findings offer, for the first time, a linkage between drug resistance and malignant transformation. Importantly, this discovery also suggests new targets for cancer drug design, such as inhibitors of protein kinase C.

What impact does the evolving story of drug resistance have on drug development and clinical chemotherapy? Drug-resistant human cells are now being used in the initial screening procedures to identify new drugs likely to be effective in the treatment of cancer in man. This represents a major change from the previous screening system that used a highly drug-sensitive mouse leukemia as the primary screen. A second reason for using human tumors grown in culture is that this system allows for screening of each candidate compound against multiple cell lines representing different kinds of human cancer, and so may allow identification of drugs with selective activity against a particular tumor type.

This disease-oriented drug discovery program was initiated during the past year and utilizes a bank of 30 human lung cancer cell lines, grown in culture, in the initial drug screen. It is planned to expand the new disease-oriented drug discovery project to screen for new drugs useful in the treatment of other solid tumors such as colon, ovarian, breast, pancreatic, and central nervous system malignancies.

While clear potential exists for improving drug discovery and clinical treatment through a better understanding of drug resistance, we must at the same time identify entirely new approaches for cancer treatment. Because of the rapid advance of knowledge in tumor cell biology, unique features of the malignant process can now be exploited for therapeutic benefit. For example, cancer cell proliferation is now known to be controlled by growth-promoting peptides and hormones. In particular, using cell lines derived from patients with small-cell lung cancer, it has been discovered that these cancer cells produce hormones that are capable of stimulating the tumor's own growth. One of these autocrine growth factors has been identified by NCI investigators as bombesin, a small protein that stimulates the growth of small-cell lung cancer in culture as well as in experimental animals. Monoclonal antibodies have been raised against bombesin and are capable of inhibiting tumor growth. These findings have led to a novel clinical trial, beginning this year, using antibombesin monoclonal antibodies in patients with small-cell lung cancer.

Another strategy in exploiting the discovery of growth factors involved in tumor cell proliferation is the development of antibodies to the growth factor receptor itself. Antibodies to the Interleukin-2 receptor of human T cells have been linked to a potent bacterial toxin, and for the first time this type of conjugate was used with early success in the treatment of patients with T-cell leukemia.

The discovery of the growth factor Interleukin-2 (IL-2) by Dr. Robert Gallo and colleagues of NCI, and its molecular cloning has allowed investigators to generate lymphokine-activated killer (LAK) cells that seek out and selectively destroy tumors in experimental animals. This research - called adoptive immunotherapy - was recently introduced in the treatment of patients with advanced cancer and will be discusses in greater detail in the clinical treatment section. However, preclinical research is continuing on this important new lead to improve its therapeutic effect and minimize treatment toxicities. For example, IL-2 is being encapsulated in polyethylene glycol to prolong its ability to be retained in animals. This work may allow lower, less frequent doses of the lymphokine to be effective in man, reducing treatment costs. Other research is improving the natural ability of killer cells to destroy cancer by incubating the LAK cells themselves with drugs such as prostaglandin inhibitors. Finally, the effects of LAK cells and IL-2 are being studied in combination with surgery or chemotherapy. These laboratory studies indicate that adoptive immunotherapy may be still more effective when used in combination with other cancer treatments.

A second property of the cancer cell that has become a target for therapy is failure to differentiate. In recent years there has been a greatly increased understanding of the biology of cellular differentiation. Many basic studies support the notion that cancer cells are blocked at a point in the maturational pathway. This work has direct treatment implications in that if the block could be removed by drug treatment, then the cancer cell would become more mature or non-malignant.

A number of differentiating agents have shown promising early antitumor activity. In studies completed in 1985, the retinoids, analogs of vitamin A, have demonstrated beneficial effects in patients with preleukemias, acute promyelocytic leukemia, and early cancers of the mouth, skin, and cervix. In related work, it has recently been discovered that growth factors such as IL-2 not only stimulate the proliferation of T cells but may also stimulate the differentiation of B-lymphocytes. Further preclinical efforts are being devoted to examining the effectiveness of combinations of differentiating agents such as interferons, retinoids, and chemotherapeutic agents. The future promise of this entirely new class of agents will depend on laboratory-clinical interface to identify cellular markers of differentiation from preclinical studies that have clinical applicability.

In addition to the traditional targets of cell proliferation, the new efforts to exploit and enhance the immune response, and the efforts to promote tumor cell differentiation, attention has also turned toward the therapeutic possibilities of inhibiting the process of metastasis. Recent work of Dr. Liotta at the NCI has shown that this process requires 1) attachment of cancer cells to a blood vessel basement membrane by recognition of the structural protein laminin; and 2) digestion of the basement membrane by specific enzymes. It is possible to block each step and so inhibit tumor cell spread. For example, during the past year small fragments of laminin have been synthesized that can block the tumor cell's laminin receptor and thus prevent attachment. Pretreatment of animals with laminin fragments has successfully prevented tumor cell spread in experimental animals, and a clinical trial of this novel treatment approach is scheduled in patients this year.

Clinical Treatment Research - A 1987 estimate of $180,807,000.

A major objective for our clinical trials program in 1987 will be the refinement and large-scale testing of the LAK cell approach. The major obstacle to the development of successful adoptive immunotherapies has been the availability of appropriate cells for use in actual adoptive transfer. During the past year, this obstacle was overcome by generating LAK cells in culture by exposing patients' white blood cells to high concentrations of T-cell growth factor, or IL-2. These cells can then be re-infused into the patient with high doses of systemic IL-2.

As mentioned previously, this treatment has been given to patients with malignancies for which standard therapy had failed. Twelve of 32 patients responded to LAK cells and IL-2, with one patient achieving a complete clinical response. This represents the first successful application of adoptive immunotherapy and the first use of a genetically engineered protein for cancer therapy in man, particularly since the responding tumors, including cancers of the colon and kidney, and malignant melanoma, are quite unresponsive to traditional therapy. National trials to expedite the testing of IL-2 and LAK are being planned. In addition to studies that will attempt to replicate initial results, developmental projects of highest priority include: 1) definition of the types of cancer responsive to LAK cells and IL-2; 2) testing of LAK cells and IL-2 in the adjuvant setting where tumor burden is smallest and likelihood of cure increased; 3) refinement of methods of harvesting and activating LAK cells; and 4) the testing of LAK cells in combination with chemotherapy, an approach highly successful in animals. In addition, it will be important to study the effectiveness of regional adoptive immunotherapy in patients with appropriate cancers. For example, the NCI is planning studies in which LAK cells are administered intra-abdominally to patients with ovarian cancer. This local approach to immunotherapy will allow increased concentration of killer cells and lymphokine at the actual tumor site.

In order to expedite clinical treatment research and make it available nationwide, the NCI supports a number of integrated clinical cooperative groups that perform coordinated cancer research. Within broad parameters, each group may pursue research approved by its members, who are the nation's preeminent experts in a particular disease or treatment, and by the NCI. Recently, collaboration between Cooperative Clinical Trial Groups has increased, and the resulting "Intergroup Studies" can provide even greater efficiency and economy of scale. The pooling of scientific talents, patient resources, and statistical expertise results in a clinical trial instrument of unprecedented strength for solving problems in pediatric cancers, interferon therapy of lymphoma, new hormonal therapy for prostate cancer, and studies in bone marrow transplantation. Selected intergroup studies include:

Intergroup Study	Treatment Strategy
Prostate Cancer Intergroup Study	Investigate the role of complete pharmacologic blockade of male hormones in prostate cancer treatment using newly available hormone agonists and anti-androgens

Intergroup Study	Treatment Strategy
Colon Cancer Intergroup Study	Investigate the role of combined adjuvant chemotherapy and immunotherapy in patients with advanced stage, but potentially curable colon cancer
Head and Neck Cancer Intergroup Studies	Investigate innovative combination of surgery, radiotherapy and chemotherapy for patients with poor prognosis, but potentially curable cancer
Melanoma Intergroup Study	Compare surgical approaches to loco-regional disease
Acute Leukemia Intergroup Study	Investigate the role of differentiating agents and novel Ara-C treatments in patients with acute leukemia

The Cooperative Groups disseminate new approaches to cancer treatment to a broad patient population. These Groups can definitively answer important questions such as the role of adjuvant therapy in selected diseases in trials requiring large numbers of patients. The positive adjuvant treatment studies in breast cancer, rectal cancer, colon cancer, and adenocarcinoma of the lung reported during 1985 have the potential of saving thousands of lives each year. In addition, the recent National Surgical Adjuvant Breast Project Cooperative Group trial, involving thousands of women nationwide, confirmed that breast-sparing surgery in combination with radiotherapy is a rational alternative to mastectomy for women with breast cancer. Thus, alternatives to standard mastectomy can be offered for the treatment of the most common cancer in American women. Other cooperative trials are investigating the prognostic significance of genetic and cell-surface correlates for patients with leukemia and lymphoma. These sophisticated biomarkers are allowing treatments to be custom-designed for patients with good or poor prognosis disease. Bone marrow transplantation, which allows the use of higher and potentially curative drug doses in patients, is also being studied by the cooperative groups. Review of the promising results of biological response modifiers using interferon has led to critical studies for new research in chronic myelogenous leukemias, hairy-cell leukemia, and non-Hodgkin's lymphoma. In addition, a definitive trial on the role of the non-specific immunostimulant BCG for the prevention of recurrence of superficial bladder cancer is planned.

Finally, in an attempt to interface between laboratory and clinic using effective drug combinations, patient studies are planned to develop clinical trials based on biochemical modulation. That is, clinical trials will be undertaken to test whether combinations of drugs based on laboratory demonstration of interaction at the biochemical level can produce similar perturbation in the patient's cancer and result in improved therapeutic results.

NCI-supported clinical treatment trials are effectively applying the advances of basic cancer biology to the problem of curing cancer. Today, over 5,000 cancer physicians involved in NCI trials follow 75,000 patients annually and see an additional 200,000 patients with cancer each year. These trials increasingly reflect the progress in basic research, and are made possible through the coordination of preclinical drug development and a nationwide network of cancer centers, outreach programs, community clinical oncology programs, and cooperative groups, supported by NCI programs.

Nutrition - A 1987 estimate of $2,482,000.

Although the primary thrust of nutrition research at NCI relates to the role of micronutrients and macronutrients in cancer prevention, important new leads will be followed in nutritional treatment research. Recent studies in molecular biology have identified a peptide secreted by tumors which can result in loss of appetite and weight in the host. This peptide, cachexin, represents an important therapeutic target for reversal of weight loss often seen in patients with advanced cancer. For example, monoclonal antibodies to cachexin might block the effect of the weight loss factor. Just as important, basic studies of cachexin and its mechanism of action will be critical in giving a better insight into why patients continue to lose weight even with only a small amount of cancer. Cachexin is even more intriguing since it is suspected as being linked to tumor necrosis factor, a naturally-occurring protein which seems to kill cancer cells without harming normal ones.

Clinical studies in patients with cancer are attempting to determine whether aggressive nutritional support by providing essential proteins, fats and vitamins intravenously will improve a patient's response to various cancer treatments, including chemotherapy, surgery and radiation. It is hoped that this would also facilitate healing and tolerance of undesirable side-effects of treatment. In addition, the nutritional status of the patient will be studied in relation to the immune system and its ability to prevent the spread of cancer.

Epidemiology - A 1987 estimate of $1,481,000.

Work will continue to analyze cancer patient survival for the general population with particular emphasis on monitoring changes in survival over time to assess the impact of treatment improvements. In addition, significant effort will be directed to developing statistical methodology appropriate for application to population intervention trials aimed at reducing incidence of specific cancers. Also, statistical support and consultation for clinical trials of lung and brain cancer will continue to be provided.

Rehabilitation Research - A 1987 estimate of $3,813,000.

Future initiatives in cancer pain management will include studies focusing on optimum pain management techniques and studies in the measurement of "quality of life" in patients with cancer pain.

Studies will continue to be conducted to identify and test interventions to reduce morbidity and the social, psychological, physical, and economic consequences of cancer for patients and their families.

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Studies will be supported on ways to improve the quality of life for cancer survivors and their families, including childhood cancer patients and employment and insurance issues.

The concrete needs of cancer patients and ways of removing obstacles to effective care will continue to be investigated.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Research

PROGRAM ACTIVITY	1986 Approp-riation	1986 Available After Sequestering	1986 Revised Estimate	Total
Cause & prevention......	$304,895,000	$290,319,000	$288,319,000	$285,733,000
Detection & diagnosis...	80,755,000	78,143,000	77,643,000	78,172,000
Treatment..............	384,972,000	367,733,000	365,333,000	365,128,000
Cancer biology..........	258,686,000	248,021,000	246,121,000	241,857,000
Total..................	$1,029,308,000	$984,216,000	$977,416,000	$970,890,000
Impact Data				
Research projects				
Number................	3,014	3,014	2,940	2,924
Amount................	$581,438,000	$556,583,000	$549,783,000	$537,134,000
Other research				
Organ systems				
Number................	1	1	1	1
Amount................	$1,000,000	$957,000	$957,000	$800,000
Coop clinical research				
Number................	252	228	228	228
Amount................	$50,204,000	$48,045,000	$48,045,000	$49,884,000
Minority biomed support				
Number................	43	40	40	42
Amount................	$3,400,000	$3,254,000	$3,254,000	$3,400,000
Other research related				
Number................	34	33	33	30
Amount................	$3,440,000	$3,292,000	$3,292,000	$3,161,000
Subtotal, other resch				
Number................	330	302	302	301
Amount................	$58,044,000	$55,548,000	$55,548,000	$57,245,000
Total, research grants				
Number................	3,344	3,316	3,242	3,225
Amount................	$639,482,000	$612,131,000	$605,331,000	$594,379,000
Research & development contracts				
Number................	449	435	435	435
Amount................	$141,506,000	$135,532,000	$135,532,000	$133,960,000
Intramural research.....	$194,847,000	$185,704,000	$185,704,000	$190,291,000
Research mgmt & supp....	$51,796,000	$49,224,000	$49,224,000	$50,635,000
Cancer prev & control...				
Number................	11	11	11	11
Amount................	$1,677,000	$1,625,000	$1,625,000	$1,625,000
Total, NCI				
Number................	3,804	3,762	3,688	3,671
Amount................	$1,029,308,000	$984,216,000	$977,416,000	$970,890,000

National Cancer Institute

Resource Development

1987 Authorization: Indefinite.

Budget Authority:

1986 Appropriation	Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$135,627,000	$129,846,000	$129,846,000	$123,888,000	-$5,958,000
		(FTEs: 20)	(18)	(-2)

Cancer Centers

Purpose and Method of Operation

Cancer centers supported by the NCI are an important resource for the total National Cancer Program established by the National Cancer Act of 1971. Spread across the country, the centers serve as sites for excellence in scientific leadership for basic, clinical, and cancer control research. With the constant advancement in scientific knowledge, they contribute to maintaining cancer programs and shaping opportunities to advance understanding of cancer. Cancer centers foster interdisciplinary research bridging the classical departmental and disciplinary barriers that may exist in research institutions. The centers promote multi-disciplinary investigation to improve the diagnosis, care, and treatment of patients with cancer.

Cancer centers core grant support from NCI provides for program leadership, centralized research instruments, and facilities not otherwise available through traditional research grants. Thus, this support provides cohesion for these institutions and enables the cancer centers to develop timely and exploratory programs at the cutting edge of research to meet our nation's health needs. The environment of the cancer centers facilitates scientific communication, provides for a well-coordinated scientific approach, and is responsible for attracting productive cancer investigators.

The cancer centers serve as the linchpin in achieving NCI goals for a 50 percent reduction in cancer mortality. They are the foci of basic and clinical research. They establish regional programs in prevention - screening and early detection. They serve as demonstration models for state-of-the-art treatment. They serve as foci of education for populations in their areas, for the medical community and for academic programs. Discoveries in basic concepts of immunotherapy and utilization of biological response modifiers such as the recent work by Rosenberg (NCI) utilizing Interleukin 2 and LAK cells can be swiftly confirmed in these centers. The cancer centers are in uniquely advantageous positions to involve particular study patients and disseminate advances in their regions.

Rationale for the Budget Request

The 1987 budget estimate of $83,465,000 represents an increase of $196,000 from the 1986 estimate. The program plans for 1987, along with expected accomplishments, are as follows:

During FY 1986, 57 cancer center core grants were supported. The current budget figure for FY 1987 will allow NCI to support 57 centers, including new centers. The peer-review process provides an ongoing critical evaluation of all centers and their individual effectiveness in relationship to the overall NCI goals. Only those centers with superior priority scores are funded.

In addition to underserved geographic areas there are underserved minority populations: the relatively inferior survival rates among blacks attests to this problem. A planning grant application for a minority (black) consortium has been reviewed and has received an excellent priority score. Funding of this grant should facilitate development of a cancer center specifically oriented towards research addressing minority cancer issues.

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Research Manpower Development

Purpose and Method of Operation

The Research Manpower Development program is designed to facilitate the discovery of new knowledge and rapidly apply it to cancer prevention, detection and treatment by providing training support at the pre- and postdoctoral levels in the basic and applied sciences and by supporting health professional education program~~s~~ designed to improve cancer curricula in medical, dental, public health, and nursing schools. The institutions and individuals who compete and qualify for grant support are expected to become the nation's most important source of future research physicians and academicians.

The National Research Service Award (NRSA) program helps prepare pre- and postdoctoral individuals to become highly competent researchers and undertake increasingly complex investigations into the cause, prevention, detection, diagnosis, and treatment of cancer. Support is provided to individual research trainees through fellowships and to institutions through research training grants. The NRSA program currently emphasizes research training in preventive oncology, nutrition, epidemiology, biostatistics, surgical oncology, radiation oncology, the cancer control sciences, and the research training of physicians and oncology nurses.

The Research Career Development Award (RCDA) program provides investigators of unusual promise with support for five years of advanced training so that they may proceed as quickly as possible into highly productive, independent research careers in basic or applied cancer-related sciences. Preventive Oncology Academic Awards (POAA) provide support for individuals who are furthering their careers in that area and also serve to consolidate preventive oncology efforts at their affiliated institutions. Clinical Investigator Awards (CIA) support post-M.D. research training, especially in surgical oncology, radiation oncology, epidemiology, nutrition, and psychiatry.

The Clinical Cancer Education Program (CCEP) which provides curricula support for cancer education at medical, dental and nursing schools will be supported.

Rationale for the Budget Request

The 1987 budget estimate of $40,423,000 represents a decrease of $2,608,000 from the 1986 estimate. The program plans for 1987, along with expected accomplishments, are as follows:

National Research Service Awards - A 1987 estimate of $28,610,000.

Research training will be broadly supported in cancer cause, prevention, detection, diagnosis, and treatment. Postdoctoral fellowships and research training grants will support training positions in basic and applied cancer science. Emphasis will continue to be placed on training cancer nutritionists, epidemiologists and biostatisticians who focus on the identification of how environmental factors affect the incidence and prevalence of cancer. Investigators in cancer detection and diagnosis, particularly radiation diagnostics, will be trained in identifying cancer at its earliest stage. Research training will be provided to investigators interested in the treatment of cancer patients and their subsequent restoration to productive lives. Particular attention will be given to the need for more surgical oncologists and radiation therapists trained in research. It is also important that NCI maintain its success in recruiting significant numbers of M.D.-trained researchers for both basic and applied research. NCI continues to support predoctoral research training for oncology nurses.

In 1987, 1,193 trainees will be funded, a decrease of 38 from 1986.

- Research Career Programs - A 1987 estimate of $6,907,000.

Nine Preventive Oncology Academic Awards will be funded this year. The new Clinical Investigator Award program, which will increase the number of post-M.D.s in cancer research, will continue. It is estimated that there will be 51 active awards of this kind along with 62 Research Career Development Awards.

The total estimate for Research Manpower Development program also includes $2,506,000 for management and support costs, as well as $2,400,000 for the Clinical Cancer Education Program.

Construction

Purpose and Method of Operation

The Construction Program provides grant support for construction of new, and the renovation and upgrading of existing, extramural cancer research facilities. NCI Construction grants assist in providing modern and safe research facilities at cancer research laboratories for the accomplishment of cancer research (basic and applied) involving hazardous chemicals, viral agents and genetic materials as well as animal facilities. These materials have major known properties which require highly specialized hoods, containment and personnel protection.

The program provides research facility support across all NCI research thrusts and also supports construction and renovation efforts of NCI facilities in Bethesda and at the Frederick Cancer Research Facility in Frederick, Maryland.

The Construction grant program provides no more than 50 percent of the total construction funds for a construction project; the remaining funds are provided through local, state, community, or university resources.

Rationale for the Budget Request

The 1987 budget estimate does not include any funds for construction. This is a decrease of $3,546,000 from the 1986 estimate.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Resource Development

PROGRAM ACTIVITY	1986 Approp-riation	1986 Available After Sequestering	1986 Revised Estimate	1987
Cancer centers support.......	$87,012,000	$83,[illegible],000	$83,269,000	$83,465,000
Research manpower development	44,963,000	43,031,000	43,031,000	40,423,000
Construction................	3,652,000	3,546,000	3,546,000	0
Total........................	$135,627,000	$129,846,000	$129,846,000	$123,888,000
Impact Data				
Research Centers				
Number....................	58	57	57	57
Amount....................	$85,823,000	$82,132,000	$82,132,000	$82,282,000
Other research				
Research career programs				
Number....................	122	117	117	122
Amount....................	$6,907,000	$6,610,000	$6,610,000	$6,907,000
Clinical education program				
Number....................	52	52	52	33
Amount....................	$4,700,000	$4,498,000	$4,498,000	$2,400,000
Total, research grants				
Number.....................	232	226	226	212
Amount.....................	$11,607,000	$11,108,000	$11,108,000	$9,307,000
Training				
Individual awards				
Full-time training slots..	204	195	195	189
Amount....................	$4,626,000	$4,427,000	$4,427,000	$4,292,000
Institutional awards				
Full-time training slots..	1,082	1,036	1,036	1,004
Amount....................	$26,212,000	$25,085,000	$25,085,000	$24,318,000
Total training				
Full-time training slots...	1,286	1,231	1,231	1,193
Amount.....................	$30,838,000	$29,512,000	$29,512,000	$28,610,000
Research mgmt & support......	$4,159,000	$3,980,000	$3,980,000	$3,689,000
Construction				
Number.....................	2	2	2	0
Amount.....................	$3,200,000	$3,114,000	$3,114,000	$0
Total, NCI				
Number.....................	234	228	228	212
Amount.....................	$135,627,000	$129,846,000	$129,846,000	$123,888,000

National Cancer Institute

Cancer Prevention and Control

1987 Authorization: Indefinite.

Budget Authority:

1986 Appropriation	Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$66,075,000	$63,213,000	$63,213,000	$63,311,000	$98,000
		(FTEs: 151)	(151)	(--)

Cancer Prevention and Control

Purpose and Method of Operation

Cancer Prevention and Control is the link between the basic and clinical biomedical research programs of the NCI and practice across the United States. The latter itself involves applied research, referred to as "Cancer Prevention and Control Research". The Congressional mandate for the Cancer Prevention and Control Program requests the Director for the Institute to "establish and support demonstration, education, and other programs for the detection, diagnosis, prevention, and treatment of cancer and for rehabilitation and counseling respecting cancer" (National Cancer Act, Section 403). The fundamental scientific leads to reduce cancer mortality and morbidity are derived from the basic and clinical research supported and conducted by the Cause and Prevention, Detection and Diagnosis, Treatment, and Biology programs, while it is the mission of the Cancer Prevention and Control Program to develop the means and methods to apply these research results in health care practice.

The NCI strategy for meeting/carrying out this mandate rests on the concept of cancer control as activities directed toward preventing cancer, detecting cancer early at the stages at which it is most effectively treated, treating the disease with regimens optimally matched to the cancer site, stage and patient condition and, finally, enabling the patient to resume a normal life as rapidly as possible. This model of cancer control is compatible with the two-stage model of cancer development (cancer develops in two or more steps, a first or initiation stage which starts the process, and a much longer promotion stage) which underlies much of the basic research now underway on the causes and early detection of cancer. (This two-stage model is discussed in more detail in the Cause and Prevention Research section of this document.) Recently, more emphasis has been placed on the promotion stage, since everyone has been exposed to initiators, and addressing promotion could have benefits for cancer prevention in people who already are middle age or older. Ideas or leads that relate to the promotion stage are translated into intervention strategies in cancer prevention and control and evaluated with scientific rigor before they are recommended for introduction into medical practice.

For example, the classic compounds known as retinoids, related to vitamin A, are now known to act through surface receptors that interact with tumor promoters and some oncogene products. As part of the Cancer Prevention and Control Program, human cancer prevention clinical trials are underway to see if these compounds will reduce the frequency of cancer in people, as is suspected from the basic research studies.

One aspect of the diet and nutrition research underway in cancer prevention and control is to determine the effect of retinoids in reducing the incidence of some cancers, particularly, lung, gastrointestinal and basal cell carcinomas. This research goes on in parallel with, and in coordination with the fundamental research to understand the mechanism by which the retinoids may influence the development and promotion of cancer.

The primary mission of the Cancer Prevention and Control Program is to reduce cancer incidence, morbidity and mortality. This can be accomplished by reducing or eliminating exposure to substances known to initiate or promote cancer such as cigarette smoking, reducing exposure to substances known to promote cancer such as a high-fat diet, increasing the percent of persons who follow recommended cancer screening practices, or increasing the percent of cancer patients who receive state-of-the-art treatment.

To identify effective strategies to accomplish the cancer control mission requires an organized, systematic intervention research program. Accordingly, NCI has developed a strategic decision making process in which all prevention and control research is classified according to an orderly sequence of five phases: (I) Hypothesis Development; (II) Methods Development; (III) Controlled Intervention Trials; (IV) Defined Population Studies, and(V) Demonstration and Implementation Studies. At the end of each phase, there is a "decision point" at which criteria are reviewed to determine if research results are adequate and sufficiently promising to warrant proceeding to the next phase. The use of this process assures that NCI gives priority to research and intervention methods that have the greatest promise to reduce morbidity and mortality for the nation.

Phases I and II, Hypothesis Development and Methods Development, represent, respectively, the identification of research leads from basic laboratory, epidemiologic, and clinical studies. The assessment of factors and outcomes which must be monitored in subsequent intervention studies to ensure that accurate and valid procedures are available before the actual study is begun.

In Phase III, Controlled Intervention Trials test the hypotheses developed in Phase I, using the methods validated in Phase II. The Phase III studies test the efficacy of specific interventions. If a cancer prevention approach or other intervention successfully passes Phase III, it may, depending on issues of potential impact, priorities and fiscal constraints, move to Phase IV, Defined Population Studies. Phase IV studies allow the impact of an efficacious intervention to be quantified by applying it in a carefully controlled study of a defined population (that is, a population representative of a particular group). A Phase IV study is conducted in a large, distinct, and well-characterized population chosen in such a way that the study subjects are representative of, and therefore the results can be extrapolated to, the ultimate target population. The Demonstration and Implementation studies in

Phase V introduce the now proven intervention to the community at large and measure the public health impact. To ensure that the intervention is applied uniformly with the validated methods, a system of evaluation and quality control procedures must be in place. These studies may be part of other public health program efforts, but evaluation and quality control procedures are still required.

Phase V programs are conducted only after careful research studies in each of the preceding phases provide results that justify demonstration and implementation. Therefore, at the completion of Phase V, a proven intervention with the demonstrated public health benefit of reducing cancer incidence, morbidity, or mortality would have been introduced in a population with known characteristics, and a process for monitoring the impact of the program would be in place.

The Cancer Prevention and Control Program consists of three major components: Cancer Prevention, aimed at developing the means and methods to prevent cancer, for the population at large or for selected groups at high risk; Cancer Control Science, in which the primary attention is research on cancer control intervention strategies and their impact on large, defined populations, as well as research on facilitating the widespread use of proven health promotion strategies; and Community Oncology, which focuses on ways to increase the survival and decrease the morbidity through community-based oncology research directed toward providing optimal care in the community, from early detection and diagnosis to state-of-the-art treatment, utilization and continuing care.

NCI has established objectives for cancer prevention, screening and treatment which help aim the cancer prevention and control program toward taking the most effective steps to reduce cancer mortality. These objectives are to be met through the simultaneous use of three strategies: 1) through research, both basic and applied, to identify the means of preventing some cancers, detecting other cancers early, and developing and evaluating effective treatment regimens; 2) through evaluation of effective cancer control technologies, and through their transfer to the health care community through the education of health professionals and the public; and 3) through cancer control surveillance to identify poor mortality, incidence or survival performance in particular geographic areas, specific population groups such as minorities, as well as to identify the cancer control resources necessary to address these issues.

The objectives concern four principal areas. First, prevention objectives were established related to smoking and diet to enhance public knowledge about behavior that can greatly reduce the risk of cancer. Second, screening and detection objectives for those cancers for which screening technologies are now available. Third, treatment objectives are addressed to bring survival results across the nation up to that level already achieved in the best treatments evaluated through clinical trials. A fourth group of objectives address cancer surveillance and focus on recommendations for information feedback and evaluation of the Cancer Prevention and Control Program's impact, particularly the impact on cancer mortality. In addition to formulating objectives, the Program has identified potential Federal, State and community actions, programs and initiatives available to support these objectives.

The core component of the NCI cancer surveillance system is the Surveillance Epidemiology and End Results (SEER) Program which gathers incidence and survival data on all cancer cases in defined geographic areas representing some 12 percent of the United States. The SEER figures recently indicated the first downturn in lung cancer incidence in white males in more than half a century; strong evidence of the impact of the change in smoking behavior on lung cancer.

The SEER program, begun in 1973, has now been in operation for sufficient time to allow consistent estimates of cancer patient survival changes. The vast potential of the SEER program is just now beginning to be realized as the data collected over the past decade has begun to mature. Studies of differences in incidence and survival among populations are valuable in directing the NCI cancer control program and providing new research leads. Monitoring trends in cancer incidence and survival continues to be important to the NCI's programs.

The SEER data (1985) indicates that for those who develop cancer, the prospects continue to improve. A decade of data from the SEER program continues to show that significant gains in survival have occurred and have been maintained for a number of cancer sites including Hodgkin's disease, the major cancers affecting children, and testicular cancer. Of major significance is a newly recognized decline in breast cancer mortality among women under 50 years of age, which is likely due in part to the use of chemotherapy in this group, a treatment recently endorsed through a consensus conference at the National Institutes of Health. The conference also noted that the relatively new hormonal treatment, tamoxifen, is recommended for many women over 50 years of age and that together these treatments have the potential to reduce the mortality rate more than 20 percent among treated women with breast cancer.

Overall, cancer five-year relative survival is now at approximately 50 percent for white Americans and 37 percent for black Americans who have shown a slight decrease in survival in the latest figures, probably due to the increasing influence of lung cancer mortality on the overall statistics. The five-year relative survival rate approximates long-term survival for most cancer sites and is therefore a measure of cancer curability.

New opportunities in cancer surveillance are emerging. An increasing trend in the United States is the development of cancer registries, which generally monitor incidence rates in defined populations or in large parts of states. The opportunity for the NCI to play a coordinating role in the development of these databases is an important one. The development of additional technical assistance and guidance may yield the further opportunity to utilize these data to augment the SEER program in its challenge of monitoring cancer in the U.S. population.

Another new development of particular importance to the cancer control effort is increasing the NCI's ability to study cancer risk factors and health behaviors which affect cancer risk. In the past, the NCI relied on infrequent surveys conducted by contractors or by the private sector. In calendar year 1987, the NCI will collaborate with the National Center for Health Statistics in its annual National Health Interview Survey (HIS). The NCI cancer control supplement to the HIS will allow for the collection of information in 52,000 households on cancer risk factors; cancer screening behaviors; and knowledge, attitudes, and behaviors related to the control of cancer. This survey will be the beginning of standardized methods to monitor the nation's progress toward accomplishing the mortality reduction objectives set by the NCI.

As a link between practice and research, SEER and the other cancer surveillance activities provide opportunities for research on the early detection and treatment of cancer, as well as opportunities for research on the causes of cancer. Moreover, the cancer surveillance system provides the link between State and local surveillance programs and the NCI-based national coordination of cancer control. For example, 10-year SEER data shows an improving trend in colon and rectal cancer (decreasing mortality despite increasing incidence). The reasons behind this trend are not clear at present; however, research using the surveillance system will allow specific hypotheses to be explored including earlier detection of the cancers and better patient management. Similarly, the trend in prostate cancer (rapidly increasing incidence with a significant increase in mortality only in the highest age groups) may indicate increased diagnosis of non-aggressive disease with implications for recommended care and patient prognoses. It is particularly important to note that the SEER program has matured to the point that the analysis of 10-year survival data is possible, and over the next decade survival evaluation of 20 years will be possible, with significant implications for research on breast, prostate, colon, and the childhood cancers.

Smoking, Tobacco and Cancer Program

Fifty-four million Americans - one in every three adults - smoke cigarettes regularly. Over six million teenagers smoke on a daily basis. More than 100,000 preteenagers are habitual smokers. To address both the human and the economic cancer-related costs associated with cigarette smoking and tobacco use, the NCI has established the Smoking, Tobacco and Cancer Program (STCP) to serve as the focal point for NCI's research, disease prevention, and health promotion activities related to tobacco use and cancer. The goal of the STCP is to decrease the incidence of cancer caused by, or related to, smoking and the use of tobacco products.

Although etiological research investigating the carcinogenic effects of smoke exposure are essential activities in the STCP, one of the primary means by which NCI's goal to reduce cancer incidence is being addressed is through a number of controlled intervention trials aimed at reducing the prevalence of smoking and tobacco use. Each of these trials is testing cost effective, durable, generalizable, and readily adoptable interventions to aid specific target populations to either stop, or not start, smoking and tobacco use. Currently, the STCP is supporting intervention trials in a number of major areas: adolescent smoking prevention, self-help and media smoking cessation strategies, utilization of physicians and dentists as intervenors in smoking cessation, prevention and cessation of smokeless tobacco use, interventions in minorities particularly blacks and Hispanics, in women and heavy smokers. Approximately 10 million Americans are now being exposed in some way to these activities.

Rationale for the Budget Request

The 1987 estimate of $63,311,000 represents an increase of $98,000 from the 1986 estimate. The program plans for 1987, along with expected accomplishments, are outlined by the major program components: 1) Prevention; 2) Cancer Control Science; and 3) Community Oncology.

Prevention - A 1987 estimate of $16,080,000.

Cancer prevention research seeks to advance knowledge on ways to reduce the risk for cancer. The overall goal is to reduce cancer incidence or progression through applied research in the areas of chemoprevention, diet and nutrition, risk reduction in occupational settings and through activities related to smoking cessation and the reduction of use of other forms of tobacco. As the prevention information base is enlarged particularly through basic research on the genetic aberrations that lead to cancer development, there will be further research into the natural history of specific cancer. That information in turn has the potential for guiding research towards developing rational interventions that may prevent the development of cancer.

- Chemoprevention

Chemoprevention research has developed rapidly during the past few years. Chemoprevention is the study of the toxicity, metabolism, and mechanism of action of those micronutrients or synthetic chemicals that could be added to dietary intake to lower cancer risk. Epidemiologic and laboratory studies provide strong evidence that various natural and synthetic micronutrients may play a role in reducing the incidence of cancer in humans. Epidemiologic studies indicate that persons eating diets high in particular micronutrients have a lower incidence of certain cancers such as lung, breast, colon, and uterine. The purpose of chemoprevention research is to determine whether these natural or synthetic agents can lower cancer incidence. Should research in the chemoprevention and diet and nutrition areas prove successful, as much as 35 percent of all cancer may by preventable. Potential chemopreventive agents include several naturally occurring substances found in many foods, such as vitamin A and its precursor, beta carotene, vitamins C and E, and the trace mineral selenium. In addition, other agents, such as phenolic anti-oxidants, protease inhibitors, prostaglandin synthesis inhibitors, indoles, and uric acid, are under laboratory study as potential chemopreventive agents.

Research of diet and cancer differs from the chemoprevention research in that the former focuses on the role of specific foods or food groups in the prevention of cancer, whereas chemoprevention focuses on the use of individual nutrients or analogs. Diet interventions take the form of modifications of dietary behavior; in contrast, chemoprevention interventions provide for the use of precise doses of chemically defined dietary supplements.

Specific objectives of chemoprevention research include:

- Identifying and characterizing agents with proven activity in preventing carcinogenesis in animals,

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- Identifying agents based on epidemiologic studies,
- Testing for efficacy and safety to select the most promising agents,
- Conducting Phase III human trials of potential chemoprevention agents,
- Applying research results to the general population.

The growing body of basic and epidemiologic evidence on the inhibition of cancer suggests that chemoprevention merits aggressive research, including human intervention trials. Such trials also are necessary to evaluate risk/benefit relationships for these agents. Phase III clinical trials and Phase III defined populations studies will provide information basic to determining the feasibility of applying given interventions to the population at large.

Human intervention studies now underway involve the use of micronutrients in defined population groups. These studies are focusing on cancer of the lung, colon, skin, cervix, and other sites. The risk groups under study include women with cervical dysplasia, heavy smokers, asbestos-exposed workers, and patients with colonic polyps, polyposis coli. For example, a study on the effect of beta carotene in preventing lung cancer among heavy smokers is in progress. Heavy smokers have a risk for lung cancer that is more than 10 times that of non-smokers. Epidemiologic studies of diet suggest that smokers who eat a diet high in beta carotene have a lower risk of lung cancer than smokers whose diet is low in beta carotene.

Other chemoprevention studies include a trial involving 22,000 physicians as subjects in the use of beta carotene for the prevention of cancer; two trials of topical retinoids for the chemoprevention of cervical cancer; and trials involving the use of various retinoids, beta carotene, and other vitamins and fiber in patients with colonic polyps. In addition, several trials are investigating the prevention of lung cancer through supplementary retinol, beta carotene, or vitamin B_{12}.

Other studies underway include an evaluation of the hypothesized protective effect of selenium with lung, breast, and bowel cancer; a case-control study to investigate the role of vitamins A, C, and E, beta carotene, selenium, protease inhibitors, fats, and fibers in inhibiting cancer of the colon and rectum. All of this research is linked to the basic research underway and the recent findings relating to the process of carcinogenesis.

Information resources for chemoprevention agents activity will continue in FY 1987. Approximately 450 agents have already been identified in the literature to have cancer inhibitory activity. An in-depth analysis of 60 of the most promising of these agents has been initiated and will continue.

A pilot study investigating the feasibility of conducting an intervention trial of micronutrients including retinol, beta carotene, vitamin E, and selenium for the prevention of lung cancer among tin miners in Yunnan, China, has begun. This group has been occupationally exposed to a number of known carcinogens, (radiation, arsenic, cigarettes) and has lung cancer rates that are extremely high. If the study is feasible, one trial will begin in FY 1987.

- Diet and Cancer

Diet and Cancer focuses its research emphasis and clinical trials on the role of foods or food groups in the prevention of cancer. In Diet and Cancer, intervention may be expressed as dietary guidelines (e.g., increase fiber containing foods; decrease fat in foods); in contrast, intervention trials supported through the Chemoprevention program may utilize pure chemicals in precise doses as test agents. The primary goal of the Diet and Cancer program is the reduction of cancer incidence through dietary modification. The expansion of knowledge regarding human nutrition and the identification of effective cancer preventive diets offer a cancer prevention approach which can be widely adopted by the general public.

Epidemiologic and laboratory studies provide strong evidence that dietary factors play a significant role in the incidence of cancer in humans, as well as in the inhibition of one or more stages of carcinogenesis in animals, particularly the promotion stage. Epidemiologic and laboratory studies have shown a correlation between dietary fat intake and the incidence of cancer of the breast, colon, prostate, and endometrium.

Epidemiologic studies and animal models show an inverse correlation between dietary fiber and the incidence of colon cancer. Dietary fiber includes a range of chemical compounds that are relatively resistant to digestion in the human intestinal tract, and may be divided into two broad classes - complex polysaccharides and phenylpropane polymers. Polysaccharide fibers are fermented by colonic bacteria and lower the pH in the large intestine, which, in turn, may alter the metabolism of carcinogens in the colon. Phenylpropane polymers are more resistant to digestion or fermentation and increase stool bulk. Their effect may be through either the dilution of fecal carcinogens, or by the absorption of carcinogens to polymers.

This epidemiologic and laboratory evidence now is converging toward a conclusion that some relatively simple dietary modifications may have a significant effect on cancer incidence and morbidity. Dietary fat is thought to be a promoter of cancer. Dietary fat intervention trials now in a feasibility stage have the potential to show whether reduction in overall fat intake can reduce the incidence of breast cancer or its recurrence among women at high risk of the disease. The National Cancer Institute is sponsoring two clinical trials to determine whether diets containing 20 percent or less of total calories from fat will reduce the incidence or recurrence rate of breast cancer. These multi-institutional trials are currently in their feasibility phases. In one trial, women at high risk of breast cancer are put on a low-fat diet and the ability of the low-fat diet to reduce the incidence of breast cancer will be evaluated. The other intervention trial would focus on women with Stage II breast cancer limited to the breast and adjacent lymph nodes and test whether the low-fat diet will delay recurrence and improve patient survival. Based on feasibility phase results, a decision will be made by NCI in consultation with its advisory boards, on the continuation to full-scale trials.

Additional research is needed to expand the base of information on the mechanism of action of different fiber components and on the distribution of these fiber components in different food groups. With this information, a dietary clinical trial may be developed with the goal of reducing the incidence of cancer of the colon through an increase in those fiber components and a reduction in dietary fat anticipated to have the greatest effect on carcinogenesis. Cancers of the breast, colon, prostate and endometrium, as well as others, may be susceptible to dietary intervention. This group of cancers constitutes more than one-third of all cancers; thus, a dietary intervention which could reduce the incidence of these cancers would have a major impact on the overall cancer incidence in this country.

Studies of vitamin A, carotenoids and dietary fibers in food are being conducted to develop methodologies for detection and for quantifying the different forms of these nutrients in selected foods. Thus, this complements the chemoprevention program by looking at food sources. These studies will aid in the interpretation of dietary studies on the role of these compounds in cancer prevention and treatment.

The physiochemical effects of dietary fiber in humans is being studied to investigate the metabolic and physiologic functions of dietary fiber and to elucidate their possible protective role in carcinogenesis.

The metabolism of retinoids and carotenoids in humans is being studied to better interpret the numerous epidemiologic studies, especially related to lung cancer, which have found a reduced risk associated with the consumption of foods high in these compounds. The pharmacokinetics of beta carotene, ingested both as a component of the diet and as a dietary supplement, are important when considering the potential preventive effects of this substance. These basic studies will help determine the optimal way of using such preventive measures.

Different diets have an effect on the production of fecapentaenes, a potent group of mutagens found in the human feces that may have a role in colon cancer. Studies to determine the influence of different diets in relation to the quantity of such mutagens in the digestive tract are essential to the understanding of its effect.

An International Food Composition Data System is being established to enhance the quality, quantity and accessibility of nutrient and non-nutrient data for future research on a worldwide basis. This comprehensive data system will provide needed information for the formulation of public policy on diet-related public health issues.

NCI is supporting two nutrient intervention trials (multiple vitamin-mineral supplements) to evaluate the relation between such supplements and esophageal cancer mortality in a population with multiple nutritional deficiencies who are at extraordinary risk for esophageal cancer. Another prevention trial testing the efficacy of daily oral beta carotene and vitamin E supplementation in the prevention of lung cancer among men who smoke cigarettes is in progress in collaboration with Finland.

Cancer Control Science - A 1987 estimate of $31,879,000.

The Cancer Control Science Program supports an integrated approach to cancer control research and applications. The focus of the research component is to develop and test interventions designed to reduce cancer incidence, morbidity and mortality. Interventions designed to reduce the incidence of cervical cancer, reduce the prevalence of smoking and tobacco use, or increase the number of primary care physicians who include cancer prevention and control activities as part of their usual office practices are examples of cancer control science research projects. The focus of the applications component is to develop and implement cancer control programs in community, medical care, workplace, and educational settings. Programs designed to assist states in designing cancer control programs, assist organizations serving minority populations in developing cancer control programs, and facilitating the integration of cancer control information into existing school curricula are examples of cancer control applications efforts. An ongoing project in the applications component is to encourage and assist the development of cancer prevention and control programs within State, local and territorial health agencies. A new program initiative has been implemented to reduce the cancer incidence, mortality and survival rates among black populations.

Cigarette smoking contributes to 30 percent of all cancer deaths; and according to the Surgeon General of the United States, it is the single most important source of preventable morbidity and mortality in our country. Although the reductions in smoking prevalence since the 1950s are encouraging and are beginning to yield a reduction in cancer incidence and mortality in American males, young females in specific age categories are smoking more. As a consequence, female lung cancer mortality has already begun to exceed female breast cancer mortality. Before the end of the century this mortality rate will continue to increase and can only be averted if adequate intervention measures are employed now. NCI will continue to emphasize intervention research to reduce the numbers of people smoking. In order to achieve reduction in smoking, NCI is targeting groups such as adolescents, minorities, women, and smokeless tobacco users, and investigating intervention strategies using self-help procedures, the media, physicians, and dentists as intervenors. Another intervention trial will be initiated shortly to implement a nationwide community-based smoking cessation program for heavy smokers. This target group is at highest risk for cancer.

Studies to identify the causes of avoidable deaths from cancer and to develop and test interventions to eliminate those causes will enter the intervention phase. Additional studies to address other causes of avoidable deaths from cancer among varied populations will enter the problem identification phase. Cancer control intervention studies being conducted through multi-disciplinary, multi-study Cancer Control Research Units (CCRU) and Cancer Control Science Program (CCSP) grants will continue. These studies are aimed at producing significant population effects on cancer mortality by investigating such areas as smoking cessation and prevention, chemopreventive agents (e.g., beta carotene), and occupational cohorts and their exposure to carcinogens.

The Cancer Control Program Tracking Database used for identifying resource allocations in key areas of intervention, will enter its data collection phase and its first summary reports will be produced and distributed for national, state and local use. Information derived from this effort will be utilized in the management and evaluation of the national effort to reduce cancer mortality.

New developmental grants to State and local jurisdictions will be awarded to plan and implement community-wide cancer prevention and control programs. NCI staff and staff of the Centers for Disease Control will provide consultation to State and local health departments on technical matters related to cancer prevention and control intervention programs.

The major intervention research initiatives to decrease the significant differentials in cancer rates between the U.S. black population and the nation's population as a whole will complete their feasibility phase and will begin to test interventions aimed at smoking prevention and cessation and the reduction of avoidable deaths from cancer. New initiatives to address the reduction of multiple risks of cancer in the black population will be implemented. NCI staff will continue to develop a research network committed to testing intervention programs for black populations. A prospective epidemiologic study, exploring factors which are thought to be important in explaining the poorer survival of black cancer patients relative to white cancer patients, will complete patient accrual. An analysis of these data is expected to help formulate cancer control interventions to modify factors contributing to the survival difference between the races.

The Cancer Communication System (CCS), a well-established resource to reach the public with information on any aspect of cancer, will continue. The activities of the CCS, including the Cancer Information Service, are aimed at changing the public's attitude toward cancer and providing a stimulus for individuals to take actions relevant to cancer control.

The Physician Data Query (PDQ) system has been available for the past two years as a resource to provide physicians nationwide with information about state-of-the-art cancer treatment for cancer patients. NCI is beginning to implement an evaluation of the distribution and effective use of PDQ by physicians and by the offices of the Cancer Information Service.

A new service of the PDQ system, called PDQ-P, is being designed as a computerized information system to facilitate the delivery of cancer prevention and screening activities during the course of typical primary care encounters. The PDQ-P concept has been successfully field tested among various primary care physician groups. Feedback from these groups is being used to tailor the system better to the needs of the practicing physician. Responding physicians have also provided considered input to NCI on effectively reaching the public with prevention and screening information.

Efforts to modify cancer risk behavior through health promotion research will be instituted via two distinct research initiatives - one for primary care physicians, another targeted for workers employed in both high-risk and non-high-risk occupations. A community-based health promotion research effort will be undertaken to increase the number of at risk women who receive regular breast examinations and mammograms. The Occupational Clinical Network, composed of 16 occupational clinics located throughout the U.S., will continue to develop prevention studies on high-risk occupational populations. The Network will bring about a critically needed standardization of procedures, protocols, and medical forms necessary for the conduct of statistically sound studies.

A potential new program to identify and characterize occupational groups of women at high risk of cancer, identify clinical research needs, and design appropriate cancer control studies is being evaluated. A workshop on high-risk women workers will be sponsored to identify and document research priorities.

Community Oncology - A 1987 estimate of $15,352,000.

The Community Oncology Program is aimed at advancing knowledge about how to decrease morbidity and increase survival through community oncology research directed toward provision of optimal care in the community, through rehabilitation research, and through continuing care interventions and through improved screening and detection techniques.

Much of the community oncology program is based on the nationwide network of cancer resources involving the NCI cancer centers. The passage of the National Cancer Act and its provision for the establishment of cancer centers for research (basic and clinical), training, and a cancer control program created a national network which now integrates basic research, research application, and patient management to combat cancer. The solid foundation forming the research network consisting of cancer centers and the community-based oncology programs 1) promote efficient interactions among researchers and practitioners; 2) serve as a focus of excellence in patient management; 3) provide research leadership for their region's constituents; and 4) emphasize the multi-disciplinary expertise required to achieve the goal of reducing the impact of cancer.

As part of its activities, the Community Oncology Program is devising ways to better facilitate studies in large population groups for early case detection studies in high-risk groups and for studies in patterns of care of patients with cancer. The Community Oncology Program also supports research in the areas of continuing care and rehabilitation for persons with cancer in order to identify and/or develop effective ways to lessen or eliminate the problems or negative consequences that may arise for cancer patients and their families.

The Community Clinical Oncology Program (CCOP) and the Cooperative Group Outreach Program (CGOP), are major cancer control efforts which link community based physicians with cancer centers and clinical cooperative groups for participation in NCI-approved research clinical trials. The programs are based on the premise that participation in clinical research protocols can provide continuing education for community physicians and will stimulate protocol quality of care for all patients treated in the community. The presence of a community program focus serves to coordinate other local cancer control efforts.

The CCOP network will be used to implement prevention trials and other cancer control initiatives. Studies will be initiated to determine if cancer management based on pretreatment multi-disciplinary planning can lead to improved cancer patient care and survival and an overall reduction in cost of treatment.

The Community Oncology Program will evaluate the impact on patient care of outreach consultation by physicians from cancer centers, universities and community medical centers who participate in tumor boards at smaller hospitals and suggest pretreatment and treatment strategies. NCI will assess various methods of technology transfer and continuing medical education techniques (such as tumor boards) to bring state-of-the-art cancer patient management to community physicians and nurses.

NCI will continue research on cancer pain and therapy. This will include studies on the transfer and utilization of optimum pain management techniques, pharmacologic studies, analysis of patient adherence to medical regimens, and role of emotional support in pain prevention. The incidence of cancer increases as a factor of age. NCI plans to support existing studies which examine the influence of old age on cancer patient workup, treatment and care. This will generate research initiatives and follow-up in promising areas of research identified for older adults who have cancer. Other studies to investigate ways to improve the quality of life for cancer survivors and their families, including recovered childhood cancer patients, and to address rehabilitation issues (e.g., employment and insurance) which affect a patient's recovery will be supported.

Consortium cancer center grants will be initiated to provide resources currently not available through center core grants for cancer centers, health departments and other health agencies to form consortia to develop cancer control research activities. Such support will give the consortium the ability to recruit staff and conduct cancer control research. Moreover, the partnership with state health agencies will provide the opportunity for transfer from the research phase to the application phase for the population at large in that region.

Selected subpopulations of the Breast Cancer Detection Demonstration Project (BCDDP) are being followed to increase our understanding of the natural history of breast cancer. Additional information will be collected to better elucidate risk factors, particularly nutritional and genetic factors in the development of breast and other cancers.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute
Cancer Prevention and Control

PROGRAM ACTIVITY	1986 Approp-riation	1986 Available After Sequestering	1986 Revised Estimate	1987
Cancer prev & control.....	$66,075,000	$63,213,000	$63,213,000	$63,311,000

Impact Data				
Research mgmt & support..	$3,874,000	$3,707,000	$3,707,000	$3,805,000
Cancer prev & control				
Inhouse..................	[illegible]	$7,258,000	$7,258,000	$7,258,000
Grants				
Number..................	95	91	91	91
Amount..................	[illegible]	$35,616,000	$35,616,000	$35,616,000
Contracts				
Number..................	60	60	60	60
Amount..................	[illegible]	$16,632,000	$16,632,000	$16,632,000
Total				
Number..................	155	151	151	151
Amount..................	[illegible]	$63,213,000	$63,213,000	$63,311,000

NATIONAL INSTITUTES OF HEALTH

Detail of Permanent Positions

	1985 Actual	1986 Estimate	1987 Estimate
ES- 4	24	24	24
ES- 3	2	2	2
ES- 2	1	1	1
Subtotal	27	27	27
GS-15	100	100	100
GS-14	166	166	166
GS-13	166	166	166
GS-12	159	159	159
GS-11	218	218	218
GS-10	3	3	3
GS- 9	238	238	238
GS- 8	40	40	40
GS- 7	205	205	205
GS- 6	187	187	187
GS- 5	118	118	118
GS- 4	66	66	66
GS- 3	25	25	25
GS- 2	2	2	2
Subtotal	1,693	1,693	1,693
Assistant Surgeon General	2	2	2
Director Grade	102	102	102
Senior Grade	61	61	61
Full Grade	33	33	33
Senior Assistant	13	13	13
Subtotal	211	211	211
Ungraded	40	40	40
Total permanent positions	1,971	1,971	1,971

TUESDAY, MARCH 11, 1986.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTES

WITNESSES

DR. CLAUDE LENFANT, DIRECTOR

DR. JAMES B. WYNGAARDEN, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. PETER FROMMER, DEPUTY DIRECTOR, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

ROBERT NAMOVICZ, EXECUTIVE OFFICER, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

JAMES WEHLING, BUDGET OFFICER, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

DENNIS P. WILLIAMS, ACTING DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICE

Mr. NATCHER. At this time, we take up the budget request for Fiscal Year 1987 for the National Heart, Lung, and Blood Institute.

And we have before the Committee, Dr. Claude Lenfant.

Dr. Lenfant, it is a pleasure to have you back before the Committee. You have been before us on a number of occasions and you always do a good job. We are glad to have you.

Before you give us your statement, tell us who you have there at the table with you, please?

Dr. LENFANT. Thank you, Mr. Chairman.

At the far left is Mr. Namovicz, who is the Executive Officer of the Institute. Next to me, on my left, is Mr. Wehling, the Budget Officer of the Institute. On my right is Dr. Frommer, Deputy Director, and of course, you know Dr. Wyngaarden and Mr. Williams.

Mr. NATCHER. Thank you very much, and we would be pleased to hear from you at this time, doctor.

Dr. LENFANT. Thank you, Mr. Chairman.

I would like to spend a few minutes to briefly underscore some of the progress that we have made this year. I should say that it has been a very productive and exciting year.

NOBEL PRIZE RECIPIENTS

First of all, as I am sure you know, two of our grantees, Drs. Brown and Goldstein, received the 1985 Nobel Prize for Medicine and Physiology as well as the Lasker Foundation award. These recognitions were made for a long series of studies on the metabolism of cholesterol. And I should point out, Mr. Chairman, that the early work of these two scientists was supported by our sister Institute, the National Institute of General Medical Sciences. Since the mid-1970's Dr. Brown and Dr. Goldstein have been grantees of our Institute.

Their work has led to the discovery of receptors on the surface of cells which have the capability of removing the so-called bad cholesterol from the blood. This year, as a further step, these scientists have cloned and sequenced the gene which is responsible for these receptors.

This work has tremendous importance toward the development of a treatment for arteriosclerosis in the genetic form as well as the so-called garden variety of this affliction.

CLOT DISSOLVING DRUGS

A year ago, Mr. Chairman, I reported to you on a new compound, a recombinant-DNA produced compound that dissolves the blood clots obstructing the coronary arteries causing a heart attack.

The preliminary data were most encouraging. Today the Institute has clearly established the efficacy of this drug. In fact, yesterday, in the Wall Street Journal, there was an article entitled, "A Clot Dissolving Drug Proves Effective in Federal Tests of Heart Attack Patients." And, as the Wall Street Journal pointed out, this drug can clear blood clots in coronary arteries in about 80 percent of patients, compared to 35 percent with other drugs.

However, there are many questions that remain to be addressed. One is how to treat the local conditions in the arteries that lead to the clot formation in the first place. We have a plan to answer this and other important questions that perhaps we can discuss later.

We believe there is a true revolution that is about to occur in the treatment of heart attacks and clinical cardiology is clearly on the threshold of a very exciting new era.

CYSTIC FIBROSIS

Turning now to the pulmonary program of the Institute, you heard from Dr. Wyngaarden yesterday about a truly giant leap forward that was made with the discovery of genetic markers linked to the cystic fibrosis gene. This discovery was made by several teams of scientists and one of them was supported by our Institute. This discovery opens the door to the next steps which are, first of all, prenatal diagnosis of the disease, the possibility of a screening test, and then identification, cloning and sequencing of the gene, and perhaps in the future, the possibility of the therapeutic genetic manipulations.

To put cystic fibrosis in perspective, I should point out that it is the most frequent lethal genetic disease and that one in 20 Americans carries the gene for this particular disease.

SICKLE CELL DISEASE

Let me now turn to our blood program. This year we have established that prophylactic penicillin prevents pulmonary infections and septicemia, which are the leading cause of death in newborn infants with sickle cell disease. Infants who are treated with prophylactic penicillin have an 80 to 90 percent reduction in infection incidence.

Clearly, this modality reinforces the need for routine prenatal diagnosis which has become available as I described last year and the year before, but which unfortunately, has not become routine in people at risk of having a child with sickle cell disease.

AIDS

Yesterday, during Dr. Wyngaarden's testimony, you asked for a progress report on AIDS research. Our Institute is supporting a major research program on transfusion transmitted AIDS. Our ongoing study which involves 200,000 donors is continuing. It will provide essential information on the natural history of transfusion transmitted AIDS.

You will hear from Dr. Fauci about the synthetic peptide which has recently been developed. This was done by a scientist supported by our Institute. This synthetic peptide replicates a fragment of the envelope of the virus and it has been found that when injected in rabbits, it can produce antibodies. This opens the door to the development of a new and very specific diagnostic test. Initial tests have begun to assess if these antibodies have the property of neutralizing the virus. In-vitro work has shown that it does. This synthetic peptide has now been inoculated into chimpanzees. Tests will soon begin to see if neutralizing antibodies develop in such an in-vivo situation. If this is the case, we have a good prospect for the development of a synthetic vaccine for AIDS.

Our programs also include the production of immunoglobin to be used for the prophylactic treatment of individuals exposed to the AIDS virus. Our efforts to neutralize the virus in blood, utilizing chemical or heat treatment, are continuing and are successful to date.

As I said at the beginning, it has been a very productive and exciting year. What is most exciting is that we see ahead of us many new ideas and opportunities for further progress.

Thank you, Mr. Chairman.

I would be glad to answer questions.

Mr. NATCHER. Thank you, Dr. Lenfant.

We will put your full statement in the record at this time.

[Information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Heart, Lung, and Blood Institute (NHLBI)

I am pleased, once again, to report to you on recent advances in the programs of the National Heart, Lung, and Blood Institute and on opportunities available in cardiovascular, pulmonary, and hematological research.

The Institute is unequivocally committed to support the entire spectrum of research, both basic and applied; both for treatment and prevention. The investment in these areas over the past year has been productive, as illustrated by the advances I will describe. Experience has shown that investigator-initiated research is the foundation of our programs and one of our richest sources of new ideas. Investigator-initiated research merits the highest priority in NHLBI planning. It is also important, however, to continue to identify and support other avenues of research, particularly clinical validation and technology transfer, such as our centers programs and clinical trials. Results of research using these mechanisms have proved invaluable in reducing morbidity and mortality from heart, lung, and blood diseases, in increasing professional and public awareness of risk factors, and in providing community practitioners of medicine with clear indications of whether certain treatments are effective.

New goals should be set in FY 1987, and new avenues of research should be pursued, with tangible implications for the prevention of disease. For example, we now know that atherosclerosis is not necessarily a part of the aging process. In fact, its onset can begin early in life. Techniques and advances in molecular biology and biochemistry will continue to expand basic knowledge about the atherosclerotic process and may lead in the foreseeable future to methods of direct intervention in this disease. The field of pulmonary research has been rejuvenated largely through basic research. For example, we now have a tenable basis for new research approaches to two forms of respiratory distress syndrome. The field of hematology, especially with regard to hereditary red cell disorders, which affect over 180 million people worldwide, has expanded during the last few years. The genetics of clotting disorders is now being clarified and leading to new insights and new treatment opportunities. Transfusion medicine is becoming a recognized medical specialty. Furthermore, we are now developing programs that link these seemingly disparate fields through common research approaches.

Atherosclerosis: Fundamental Investigations

Deaths from cardiovascular diseases account for almost one-half of all deaths in the United States, three-fourths of which are related to atherosclerosis. In our testimony two years ago we described in some detail how plasma cholesterol associated with low density lipoproteins (LDL) contributes to formation of atherosclerotic plaques. It is very gratifying to be able to report that in the fall of 1985, Michael S.Brown and Joseph L. Goldstein of the University of Texas Health Science Center were awarded both the Nobel Prize for Medicine and the Albert Lasker Medical Research Award in recognition of their work in solving the mysteries of the LDL receptor. In the 1970's, the National Heart, Lung, and Blood Institute provided support to Dr. Brown, and the National Institute of General Medical Sciences provided support to Dr. Goldstein for this work, which originated when these two scientists at an earlier date began their research careers in NIH laboratories. Since 1977, their work has been supported by the NHLBI. They have elucidated the mechanisms involved in the regulation of levels of blood lipids by receptors on the surface of the liver and other cells that breed particles of LDL and remove these from the blood stream. The LDL is taken into the cells where it is broken down and yields its cholesterol to serve the cell's needs. When the receptors are defective, LDL cannot be removed normally and it accumulates to high levels in the blood plasma. The buildup accelerates the atherosclerotic process. Mutations in one of the genes for the receptors can produce heterozygous familial hypercholesterolemia, which is a cause of heart attacks in middle-aged people. In fact, approximately one person in every 500 inherits one such mutant gene for the LDL receptor, and as a consequence may suffer heart attack as early as age 35. About one in one million persons inherits two mutant LDL receptor genes. These persons have extremely high LDL-cholesterol levels, and usually develop heart attacks before 20 years of age. Genetically induced alterations in the LDL receptor have now become the subject of intensive research.

Recently it has become possible to study the molecular genetics of these mutations as a result of the cloning of complementary DNA (cDNA) for the human LDL receptor and the subsequent isolation of genomic clones covering most of the LDL receptor gene. This information would be used to develop insights to the management of the inherited disease familial hypercholesterolemia and methods to intervene and control high blood cholesterol.

Atherosclerosis: Prevention and Education

A large body of evidence, including the results of the Lipid Research Clinics Coronary Primary Prevention Trial (CPPT) that I reported to you last year, has shown that blood cholesterol levels can be lowered safely by diet, by drugs, and by both. In light of this evidence, it is important that health professionals and the public be made aware of the significance of cholesterol as a risk factor for coronary heart disease. Recent surveys of physicians and the lay public suggest that their understanding of this critical information is inadequate. Thus, there is need for a concerted national effort to provide information both to health professionals and to the general public. A recent NIH-sponsored Consensus Development Conference on Lowering Blood Cholesterol developed guidelines for health professionals and the lay public regarding cholesterol levels that should be treated, goals of treatment, and issues relating to the use of diet and drugs. After the consensus conference, interest began to grow for a Federally sponsored National Cholesterol Education Program.

The Institute has now developed and is coordinating such a program, the mission of which is the reduction of coronary heart disease morbidity and mortality attributed to elevated blood cholesterol. This is a national educational effort involving extensive cooperation and coordination with other government agencies and intermediary groups in the private sector. The National Cholesterol Education Program will be operated as a partnership with a wide range of organizations. The effectiveness of such networking was established by the National High Blood Pressure Education Program, which also encompassed a large number of organizations -- governmental, professional, voluntary, community, private, and educational.

Neonatal Respiratory Distress Syndrome: Lung Surfactant

A lipoprotein-complex called pulmonary surfactant is present in the small air sacs of the lung. This substance reduces the surface tension of pulmonary fluids and thus greatly reduces the work of breathing. Prematurely born infants who are deficient in this lipoprotein complex can manifest a lung disease called respiratory distress syndrome (RDS). The possibility of using artificial or animal-derived surfactant for treatment of neonatal RDS is now foreseeable. Institute-supported investigators working in collaboration with private industry have recently determined the entire sequence of amino acids in canine and human surfactant proteins. Earlier this year, they cloned the gene for human surfactant. By implanting the cloned gene in cultured human cells, scientists can now synthesize large quantities of surfactant protein. In addition to their anticipated therapeutic value, these recent accomplishments will provide molecular probes for future studies to determine the structure and regulation of the gene or genes responsible for surfactant protein, make it possible for investigators to study gene expression during lung development, and generate human surfactant-associated protein for possible clinical use.

Adult Respiratory Distress Syndrome: Therapeutic Regimens

Another type of respiratory distress syndrome is the condition of acute respiratory failure that develops in patients as a sequel to various conditions, including trauma and viral respiratory infections. The high mortality rate associated with adult respiratory distress syndrome (ARDS) attests to the difficulty of finding effective treatments for this condition. The cornerstone of therapy for ARDS is mechanical ventilation with continuous positive airway pressure. Recent basic studies of the action of drugs on inflammatory cells, and experiments testing the delivery of certain enzymes to sites of pulmonary injury, hold the promise that practical, effective forms of treatment will emerge as an adjunct to ventilatory assistance. A class of drugs that may prove useful in treating ARDS are non-steroidal anti-inflammatory agents. The ibuprofen, now widely used as an analgesic, has recently been found to suppress many biological activities thought to be associated with development of acute respiratory failure.

An alternative therapeutic approach being tested is the use of systems for delivering quantities of naturally occurring antioxidants to lung tissue. Red blood cells were used as natural antioxidant "capsules" and shown to provide a remarkable degree of protection against oxidant-induced lung injury in several kinds of experiments. This research may have a significant impact on the treatment of this life-threatening disease.

AIDS

Transmission of acquired immunodeficiency syndrome (AIDS) through transfusion of blood or blood components should be greatly reduced now that tests for antibodies to the virus are being used for all units of donated blood or plasma in the United States, and positive units are carefully discarded. In addition, development of heat treatment to inactivate any virus which may escape the screening procedure has resulted in a safer product for hemophiliacs. We continue to support studies to determine what factors increase the risk that transfusion-infected individuals will develop AIDS. We also support the search for antibody fractions that might neutralize the virus, and we plan to support research on other methods to inactivate the virus in blood products.

Red Cell Disorders: Sickle Cell Anemia Treatment

The prompt institution of treatment of the child who presents with life threatening complications associated with sickle cell disease depends on early diagnosis and entry into the health care delivery system. For the system to work as efficiently as possible, a thorough education of the parents must be instituted soon after the diagnosis is made. Preliminary evidence demonstrates that infants with sickle cell anemia who receive immediate care from a knowledgeable provider, combined with measures which reduce the incidence of infection (such as prophylactic penicillin and pneumococcal vaccine) may have a lessened likelihood of early death. In the absence of specific therapy for sickle cell disease, such approaches that prevent complications and crisis offer the best opportunity for optimal care and underscore the importance of newborn screening for sickle cell disease.

Cooley's Anemia

Patients with Cooley's anemia, who must undergo lifelong treatment by transfusion of red blood cells, suffer from the toxic effects of iron accumulation in vital organs, and usually die of cardiac failure. Because transfusion with very young red blood cells (neocytes) minimizes the accumulation of iron, the separation of these young cells from frozen blood has been a scientific challenge. At one center investigators have now been able to prepare neocytes from fresh blood by using a filter to remove white cells and platelets before separating neocytes by centrifugation. Such preparations have now been used for more than 500 transfusions without any adverse reactions reported. Preliminary data also indicate that this method results in a higher concentration of red cells, a decrease in the overall number of transfusions required, and an increase in the oxygen-delivering capacity of the blood. Moreover, the yield of packed red cells and neocytes is 36 percent greater and at a reduced cost compared to use of frozen preparations. These advances hold great promise for less costly, more effective treatment of Cooley's anemia.

This nation's investment in heart, blood vessel, lung, and blood research continues to pay dividends and continues to return benefits for good health. Progress in prevention and treatment of many heart, lung, and blood diseases has been amply demonstrated in the past year.

Mr. Chairman, the 1987 budget request for the National Heart, Lung, and Blood Institute is $785,697,000. I will be pleased to answer any questions the committee may have.

LENFANT, CLAUDE, M.D.
Director, National Heart, Lung,
and Blood Institute, NIH

October 12, 1928, Paris, France

Education: B.S., University of Rennes, France, 1948. M.D., University of Paris, France, 1956.

Professional History: 1957-1958, Research Fellow, University of Buffalo, New York. 1958-1959, Research Fellow, Columbia University, New York. 1959-1960, Assistant Professor of Physiology, University of Lille, France. 1961-1965, Clinical Instructor of Medicine and of Physiology and Biophysics, University of Washington, Seattle. 19661967, Clinical Assistant Professor of Medicine and of Physiology and Biophysics, University of Washington, Seattle. 1968-1971, Associate Professor of Medicine and Physiology and Biophysics, University of Washington, Seattle. 1970-1972, Acting Associate Director, Collaborative R&D Program, National Heart and Lung Institute, NIH. 1970-1972, Associate Director for Lung Programs, National Heart and Lung Institute, NIH. 1971-1972, Professor of Medicine and Physiology and Biophysics, University of Washington, Seattle. 1972-1980, Director, Division of Lung Diseases, National Heart, Lung, and Blood Institute, NIH. 1981-1982, Associate Director for International Research, NIH. 1981-1982, Director, Fogarty International Center for Advanced Study in the Health Sciences, NIH. 1982-Present, Director, National Heart, Lung, and Blood Institute, NIH.

Professional Organizations: Association of American Physicians, American Society for Clinical Investigation, American Physiological Society, American Federation for Clinical Research, French Physiological Society, International Federation for Medical Electronics, American Society of Zoologists, Society for Experimental Medicine and Biology, Undersea Medical Society, New York Academy of Science.

Honors, Awards: Thesis Prize, University of Paris, France, 1956. Commendation Tohoku Medical Society, Sendai, Japan, 1973. Superior Service Honor Award, DHHS, 1974. Regents' Professor, University of California, Los Angeles, 1975. Testimonial Dinner, American Thoracic Society, 1979. Honorary Fellow, American College of Chest Physicians, 1979. Honorary Professor, National Yang-Ming Medical College Taipei, Taiwan, 1980. Honorary Professor, Universidad Peruana Cayetano Heredia, Lima, Peru, 1981. Senior Executive Service Performance Award, 1982. Elected Institute of Medicine, National Academy of Sciences, 1983. American.Heart Association Scientific Councils' "Distinguished Achievement Award," 1983. Senior Executive Service Performance Award, 1983. Honorary Fellow - Council on Clinical Cardiology - American Heart Association, 1984. Senior Executive Service Performance Award, 1984. Forrest M. Bird Contributory Award, American Respiratory Therapy Foundation, 1985. Senior Executive Service Performance Award, 1985.

Authorship, Editorship: Author or Co-Author of 192 scientific publications Served on Editorial Boards of: Am. Journal of Physiology; Journal of Applied Physiology; Respiratory Physiology; Am. Review of Respiratory Disease; Undersea Biomedical Research; Proceedings of Society for Experimental Biology and Medicine; Revue Francaise des Maladies Respiratories; Journal of Applied Physiology; Respiration, Environmental and Exercise Physiology; Am. Journal Am. Journal of Medicine; Continuing Education for Family Physicians; Executive Editor of 38 volume monograph series, Lung Biology in Health and Disease.

INVESTIGATOR INITIATED RESEARCH

Mr. NATCHER. Now, doctor, in your statement to the Committee, you said that investigator initiated research merits the highest priority in your Institute's planning.

Do you believe, doctor, that this priority is reflected in your budget proposals for 1986 and 1987?

What would you say about that, Doctor?

Dr. LENFANT. Well, Mr. Chairman, when considering the relevant goals of our program, which are to find treatments and prevention regimens for heart, lung and blood diseases, we view the individual research grant as the very foundation of our program. Therefore I say that yes, these research grants are essential to our programs.

But, at the same time, we have other activities which we must pursue actively and forcefully so that we maintain a balanced program, and that is a program which includes mechanisms of support other than research grants.

1986 SEQUESTRATION

Mr. NATCHER. As you know, Doctor, by sequestration, the reduction in your 1986 appropriation is $36,947,000. Of this total, $22,889,000 will come out of research project grants. Smaller amounts will come out of other mechanisms, such as research centers, training, contracts, and intramural research.

Will any of these programs be cut below the 1985 level? Will any of them go below 1985?

Dr. LENFANT. Our training programs will go below the 1985 level. The same is true for our center programs and for our contract activities that support many of the population based studies and the clinical trials conducted by the Institute.

Mr. NATCHER. Do you plan on making a request to reprogram any of the 1986 Gramm-Rudman-Hollings cuts, and if so, where would the money be used? Any indication that there might be a reprogramming request?

Dr. LENFANT. At the outset Mr. Chairman, we feel that the Institute can do lots of good things within the total budget which is recommended for us.

At the same time, we feel that the current distribution limits our flexibility to capitalize on needs and new opportunities as they arise. Therefore, it will certainly be our intent to make some requests for reprogramming to redistribute funds we have.

Mr. NATCHER. Doctor, 1986, as you know, your budget documents show that the appropriation would have permitted you to fund a total of 2,704 investigator-initiated research project grants at a total cost of $532,952,000. After the sequestration required by the Gramm-Rudman-Hollings Act, you still propose to fund 2,704 grants at a cost of $510,063,000.

How can you fund the same number of grants while cutting the cost by $22,889,000? How do you do that, Doctor?

Dr. LENFANT. Well, we do that by imposing downward negotiations on our grants. For instance, the non-competing research project grants will be negotiated downward by about 5.5 percent. While, the competing research grants, in this case, will be negotiated downward by approximately 10 percent from the study section recommended level.

Mr. NATCHER. Would you prefer to fund a fewer number of grants at a higher average cost per grant under the circumstances?

Dr. LENFANT. Well, we are concerned about a fixed number while at the same time having to impose a downward negotiation, the level of which is sometimes more than we think it should be. Basically what I said earlier with regard to the other mechanisms of support, applies as well to the research grants.

Mr. NATCHER. In addition to the sequestration of $22,923,000 for research projects, the budget, as you know, is requesting a rescission of $11,469,000 appropriated for research project grants.

How do you reconcile, Doctor, this proposal with your statement that investigator-initiated research should have the highest priority?

How do you reconcile that, Doctor?

Dr. LENFANT. Well, I do not know if I can do that to your satisfaction, nor even possibly to mine.

When we were requested to effect a rescission we were confronted with basically two alternatives. One was to make a further cut in all of the mechanisms. However as I mentioned earlier, we are very concerned about the decreases in the research centers as well as in the mechanism of support for clinical trials and population based studies. The other alternative was to further cut the research grants in order to preserve the mechanisms that I just mentioned, that is, those that had already been reduced. Therefore, we made the decision to take the rescission from the research grants.

Mr. NATCHER. Doctor Lenfant, you are an excellent director of the National Heart, Lung and Blood Institute. I have always believed that, and Dr. Wyngaarden, is a good soldier. He is really holding this budget up for you. He is a good soldier for you. Dr. Lenfant, we are going to bring you out a good bill.

Mr. Conte, I yield to you.

NUTRITION AND HEART DISEASE

Mr. CONTE. Thank you, Mr. Chairman.

Doctor Lenfant, it is always a pleasure to have you before our Subcommittee. I always feel, when I know that you are scheduled to appear, that I have to sharpen my wit a little bit just to keep up with you. There are not too many witnesses that we get that combine a complete control of the subject matter with the charm of a Maurice Chevalier the way you do, Doctor.

Doctor, the Fiscal Year 1987 budget request for the Heart, Lung and Blood Institute, is $785.7 million and that would not only take you below the Fiscal Year 1986 appropriated level, but it would also take you below the 1985 appropriated level, is that correct?

Dr. LENFANT. Yes, that is correct, Mr. Conte.

Mr. CONTE. You mentioned in your statement of the enormous cost of heart, lung and blood ailments, with deaths from cardiovascular and lung and blood diseases accounting for one-half of all the deaths in the United States and five of the 10 leading causes of the infant deaths and five of the 10 leading chronic conditions causing limitation of activity.

But in few areas has the progress in arresting them and turning around some of these statistics been as dramatic as in the cardiovascular area, where for the past 20 years, the decline in mortality has been the most important factor in increasing the life expectancy of the people of the United States.

What part do you believe that environmental and lifestyle factors play in the development of heart and lung diseases?

Dr. **Lenfant**. A very important part, especially with regard to cardiovascular diseases. I believe everybody would agree that some habits that are individually determined, as well as habits formed from social pressures, may cause cardiovascular responses which eventually can lead to disease or even death. For instance, nutrition is one example. During the last year some very important and significant observations have been made, such as relating nutrition with high blood pressure: there is no question that these two are closely related. In the United States, we estimate that approximately one-quarter of our population are hypertensive. And it is interesting that one-half of these people are considered obese or overweight. Now, if you take the other three-quarters of the population, that are not hypertensive, only 15 percent of this group are obese or overweight.

Yes, I would say the one thing that has become very clear during the last 12 to 18 months, is the role of nutrition in hypertension.

Mr. **Conte**. Therefore, if we can influence those environmental and lifestyle factors we could prevent much of the heart disease and lung diseases that people suffer today?

Dr. **Lenfant**. There is no question about that.

SMOKING PREVALENCE

Mr. **Conte**. On smoking, Doctor, and I can talk about it because I think that you have noticed, I am not puffing on a cigar, I have given it up for Lent.

Is it true that three out of four smokers who try to quit, end up smoking again within 12 months?

Dr. **Lenfant**. That is correct.

The fact is, that the population of smokers is consistently decreasing in the United States. Today, no more than 32 percent of the male population is smoking in contrast to 55 to 60 percent 20 years ago.

SALT AND HEART DISEASE

Mr. **Conte**. On hypertension, we talked before about how everyone should know their blood pressure and either have it checked or check it themselves. One of the things that you hear is how it is good to cut down on salt.

But lately it seems that the message that you get from the researchers is that some people are sensitive to salt in relation to their blood pressure, but there are others that may not be. How do you know if you should cut down on salt, for instance?

Dr. **Lenfant**. What you say is absolutely correct. There is no question that some individuals are more salt sensitive then others.

However, at this point in time, it is difficult to say that you are salt sensitive while, for instance the Chairman is not salt sensitive.

We have a research program to enable us to make this determination, however, the outcome of this research is not available yet.

In practical terms, I would submit to you that any individual whether or not he or she is salt sensitive, would do well to cut down on their salt consumption, which for some individuals, is extremely high.

Mr. CONTE. We see that as we move more and more in the direction of consumption of prepared foods and fast foods, that there is lesser chance to control salt intake.

Is the salt content of prepared fast foods something that people should be aware of and be concerned about?

Dr. LENFANT. Yes. It is absolutely correct that the fast food is usually overly salted by many standards. In fact, Mr. Conte, yesterday, I heard on the radio some very interesting comments about some fast food items that are not only high in salt content but also very high in saturated fats, and these as you know, may cause an increase in blood cholesterol.

SATURATED FATS IN CHILDREN'S DIETS

Mr. CONTE. There was a very interesting series of articles in the paper last year concerning eight of the country's largest chains of fast foods and family restaurants that cook their french fries and other foods in beef fat.

That is high in saturated fats. Are parents unwittingly exposing their children to the increased likelihood of a heart disease by allowing them to eat a lot of this fast food?

Dr. LENFANT I would say that today we do not have hard scientific evidence that would satisfy all the critics, however, I would like to speculate a little here and tell you of a study that has been reported. About six or seven months ago, a community in the south made some systematic autopsies in young people who died for whatever causes—accident or whatever the cause might have been. They found that even in individuals as young as ten years of age, there were some fatty deposits in the arteries—a clear indication that arteriosclerosis, which is the main cause of coronary heart disease and heart attack, is not something which starts developing when you are 30 or 40 years old. It is something, that in many instances, starts very early in life.

These children from this community had been followed for years and their history was well known. The association could therefore be made between the number and severity of the lesions in the arteries of these children with the kinds of eating habits that they had.

So, clearly, there is no question that the arterial lesions which lead to cardiovascular diseases and coronary disease, in particular, start very early in life.

Therefore, one can conclude that even at a younger age of life, dietary habits should be monitored and carefully considered.

CHOLESTEROL

Mr. **Conte**. We have talked about cholesterol levels before. Which would you say is more important as a risk factor, high blood pressure or high blood cholesterol? And is cholesterol the problem or is it the hardening and the narrowing of the arteries that are the cause of this?

Dr. **Lenfant**. Well, one comes from the other. Basically the hardening of the arteries results from the deposits of fatty material and calcium. The fatty material comes from an excess of cholesterol in the blood. Eventually it gets into the walls of the arteries and that is what causes the hardening that you are referring to.

Now, as to whether blood pressure or cholesterol is more important. Today both are considered to be very important, and equally important factors. In fact, there are some indications that the effect of both is more than the absolute sum, that is, there is a synergistic effect of those two risk factors.

Mr. **Conte**. I just recently spent some time in a clinic, and I was telling the Chairman, that I had a lot of time hanging around from one test to another, and I was reading everything that I could pick up and I read something there that they now have something like a blade that they can put into your arteries that will open them up and they take it out one little layer at a time.

Dr. **Lenfant**. Well, I do not know about such techniques. What we have is a catheter that can be inserted into an artery and at the end of the catheter there is a small balloon. When you put the tip of the catheter through the obstruction, you inflate the balloon and relieve the obstruction and thereby increase the lumina of the artery. It is a technique that is being used more and more. In fact, last year there were approximately 65,000 of these procedures performed in this country as opposed to 2,000 in 1979.

It is a technique which was originated in Switzerland, about 8 or 9 years ago and has turned out to be very successful. Later during the hearings if we have time, I will tell you about an aspect of this technique that relates to what I mentioned in my opening statement about the drug that clears the blood clots from the coronary arteries. There are some very interesting things that are happening today which, in the views of most cardiologists, are going to have a tremendous public health impact in the years to come and could benefit 600,000 to 700,000 people a year in this country alone.

Mr. **Conte**. Good for the patient and good for the balloon manufacturers too.

Thank you, Mr. Chairman.

Mr. **Natcher**. Mr. Stokes.

CARDIOVASCULAR DISEASE IN MINORITIES

Mr. **Stokes**. Thank you, Mr. Chairman.

Dr. Lenfant, it is always a pleasure to see you and welcome you back here.

I was struck by a statement in your formal testimony: "Deaths from cardiovascular diseases account for almost one-half of all deaths in the United States, three-fourths of which are related to arteriosclerosis."

You recall that this past October, former Secretary Heckler released a task force report on disparities between white and black health status in America.

In that report, cardiovascular disease and stroke was found to be a major cause of excess deaths among minorities. You and I have discussed the ramifications of this problem many times. But, this report also indicated that blacks still have a marked excess of hypertension, black males under age 45 are ten times more likely to die from hypertension than white males, stroke deaths among black males are nearly twice as high as among white males, and so on.

In fact, the report concludes that 60,000 excess deaths occur among minorities in six categories that were examined by this task force.

Yesterday, Dr. Malone, who chaired this task force, indicated that throughout NIH attention is being focused on the task force report and the NIH is developing responses to it.

My question Dr. Lenfant, is what are you planning to do as a result of this report, particularly, in the area of cardiovascular disease?

Dr. LENFANT. We have been, and are doing a great deal to address these particular questions.

To illustrate that, I might mention that just a few months ago, the Institute published a report on research and related activities concerning blacks and other minorities. This report describes in some detail all of the things that we have been doing, including those that were initiated last year. We had some insights before the publication of the report, because the Chairman of the panel on cardiovascular diseases was a staff member from our Institute. Our report on our research in minorities shows that between 1983 and 1985 we have doubled our support of research related to minorities.

The essence of our programs is basically to understand the very issue that you mentioned in formulating your question. Why is there an excess of deaths from cardiovascular disease in the black population?

And I wish that I could give you an answer. I cannot do that, but what I can say to you is that we have initiated a number of programs that we hope will provide the answer to your questions in the near future.

More studies are about to begin and let me illustrate that by mentioning two of them. We and the scientific community are very intrigued by the fact that when you look at death rates from cardiovascular diseases in the United States, in some states the death rate is twice as high as in some other states.

Since we want to understand this phenomenon, we have selected a few communities in the country to study it and in one of those communities the population is predominantly black. In another study we are looking at cardiovascular risk factors in young adults. In this study too, we have selected a population that is almost entirely black.

So I believe we are investigating as fast as possible the issue that you are raising.

Mr. **Stokes**. Well, I am pleased to know that there is this type of concern and that there is interest and a desire to do something about these issues. It is, obviously, a national problem. It is a serious one. It is one that frankly, disturbs me year, after year, after year, after year to have to sit here and continue raising the same questions. I have been raising these questions now for 16 years, right here on this Committee.

Hopefully the day will come when we will achieve some parity in this area.

Dr. **Lenfant**. I believe that it will come. Let me add something else that I should have mentioned and that is very important. Our Institute has been very active in working with the Association of Minority Health Professions Schools. We have developed a number of specific programs not only to foster more and better research but also to train a cadre of investigators, minority investigators, who will be able to address these problems as well.

NATIONAL CHOLESTEROL EDUCATION PROGRAM

Mr. **Stokes**. Let me talk a little bit about the cholesterol problem which was raised by Mr. Conte, and about which I have a high interest also.

Overall, can you tell me what you are doing to reduce the overall problem of coronary heart disease. I notice that you have initiated a new National Cholesterol Education Program.

Can you tell us about the program and what you hope to achieve through it?

Dr. **Lenfant**. Yes sir.

By and large, it is considered that in the United States, one-quarter of the population have a blood cholesterol level that is higher than it should be. Now, no one is thinking for one second that this one-quarter of the population should be subjected to some active treatment to lower the cholesterol. What we do believe, however, is that in many cases, individuals can take care of their own cholesterol provided they know what it is. And therefore, our message, through our education program on cholesterol is a very simple one. And that is: "know your cholesterol." If it is high, see your physician and do something about it. That can be done with little cost and no pain. There are many examples that show it works.

We want to increase the level of awareness about cholesterol. There are many people in this country who have the good fortune not to have a cholesterol problem, but unfortunately some do and we think that these people should be aware of it and should do something about it.

Mr. **Stokes**. According to the task force report to which I referred earlier, coronary heart disease rates are twice as high in black women as in white women. Are black women likely to benefit from the National Cholesterol Education Program?

Dr. **Lenfant**. Yes, although undoubtedly, things will be more difficult, as we have found with the High Blood Pressure Education Program that you are so familiar with.

Mr. **Stokes**. So it compounds the problem?

Dr. **Lenfant**. It does, but also, the level of cholesterol in people, in most cases, is a result of dietary habits, which are in effect dictated by socio-economic considerations. For that reason, it might be more difficult to effectively lower cholesterol in population groups where the socio-economic status is not as high as in other groups.

Mr. **Stokes**. Thank you very much, Doctor. Thank you, Mr. Chairman.

Mr. **Natcher**. Mr. Early, I yield to you.

1986 BUDGET

Mr. **Early**. Dr. Lenfant, your budget justification tells us, and I quote: "The development of new techniques and concepts in the neurosciences, in molecular biology, is revolutionizing the focus of basic research as it pertains to the diseases under the purview of the National Heart, Lung, and Blood Institute."

Doctor, how much of an increase is there in this year's budget, so you will be in the "thick of the revolution?"

Dr. **Lenfant**. Well——

Mr. **Early**. Well, is there an increase, Doctor, in your budget?

Dr. **Lenfant**. No.

Mr. **Early**. No. But you are telling us that there is a revolution out there, that it is exciting, and we should get in it.

Doctor, aren't there more opportunities than there were in 1985? In 1985, you were $18 million higher.

Dr. **Lenfant**. Yes, that is correct.

Mr. **Early**. Well, you are the director of the institute. How do you justify that?

Dr. **Lenfant**. Well, Dr. Wyngaarden gives me my budget. [Laughter.]

Mr. **Early**. Doctor, in 1987, you have $74 million less than you had in 1986.

Dr. **Lenfant**. That is correct.

Mr. **Early**. Don't tell us there is a revolution and there are revolutionizing opportunities, and then give us this budget.

With the amount available under the revised 1986 request you will be able to fund 69 fewer new and competing grants. Is that right?

Dr. **Lenfant**. That is correct, sir.

Mr. **Early**. For the record, tell us what areas of research would be affected by this reduction. I do not know how that is staying with the revolution.

The 1987 budget request would fund 802 new and competing grants, 84 fewer than the 1986 level, and 99 fewer than the 1985 level, a 10 percent reduction.

[The information follows:]

Grant Reductions

By supporting fewer grants, the National Heart, Lung, and Blood Institute (NHLBI) reduces the rate of acquiring fundamental and applied clinical information concerning heart, blood vessel, lung and blood diseases. It is likely that research efforts of all the national program plan areas will be affected.

Research on the major disease areas of the heart—to arteriosclerosis, hypertension, cerebrovascular disease, coronary heart disease, arrhythmias and myocarditis and congenital heart disease—will be affected. Curently, research grants identified as highly meritorious that cannot be funded include fundamental research areas of neural, hormonal and cellular factors involved in maintaining heart function; pharmacology; myocarditis; lipid metabolism and atherosclerosis research; studies of cellular and molecular control of kidney functions that affect blood pressure; and the role of calcium in hypertension; and control of blood vessel function by the nervous system.

The clinical program areas of chronic obstructive pulmonary disease, occupational and immunologic lung diseases, pulmonary vascular diseases, and pediatric pulmonary diseases as well as the program on structure and function of the respiratory system will each be involved. Progress in highly active and productive areas will be affected—molecular biology, neurobiology, biochemistry and immunology. Their application involves such clinical problems as synthesis of pulmonary surfactant for treatment of neonatal respiratory distress syndrome; identification of the gene(s) involved in cystic fibrosis that may unlock therapy for this most common genetic disease of the western world; and the molecular mechanisms regulating the antioxidant enzymes critical in the defense against intracellular toxic forms of oxygen.

Programs on blood diseases and resources that are likely to suffer from the reduced number of grants include: bleeding and clotting disorders; disorders of the red cell including sickle cell disease and blood resources affected research includes investigation of the structure on the sickle cell hemoglobin molecule that is necessary for designing drugs that can improve the health of patients with this disease; biochemical and immunologic studies of coagulation factors and defects; biochemical and immunologic studies of coagulation factors and defects; factors affecting the efficacy and systemic effects of tissue plasminogen activator; and research on posttransfusion cytomegalovirus infection.

Research will be affected not only on fundamental and clinical problems in all facets of the Institute's responsibilities, but also on the demonstration and education areas—the effective transfer of knowledge to the public and to the health professions.

Mr. EARLY. Mr. Director—and I had this discussion with Dr. DeVita this morning.

I used to see a lot more flexibility and autonomy out there. Mr. Natcher told you you are a "good soldier." But I mean, we are all in the same army. This is tough for me to accept, I will tell you.

Dr. LENFANT. Mr. Early, I believe that all of us recognize that these are difficult times, and that things just cannot be quite the way that we would like them to be.

INDIRECT COSTS

Mr. EARLY. Wait a minute, Doctor. I have got to interrupt for a minute. I do not like to do that. But let's go to indirect costs.

I have tremendous confidence in our universities throughout the United States. You know, you are making tremendous reductions in indirect costs, going to the universities. I think that choice is made at NIH, either with Dr. Wyngaarden or with Dr. Miller down in OMB. OMB is running NIH; they are running HHS, and that is disturbing to me. I think it is disturbing to a lot of people.

So my question to you is, do you believe that these indirect cost reductions should occur?

Dr. LENFANT. Well, here again, it is an action that is necessary to deal with the budget situation as it exists.

Mr. EARLY. That is the point that I make, Dr. Lenfant. No other agency, no other agency including the Pentagon, is doing this in 1986.

They are all doing it in 1987, aren't they?

Dr. LENFANT. I do not know what is going on in the Pentagon.

Mr. EARLY. Well, I have seen a brochure from the AMA that said that none of them are expected to take their reductions in 1986 except NIH. Why, Doctor?

Dr. **Lenfant**. Well, Mr. Early, I can discuss the Institute, I hope as well as you would expect, but I do not know that I can really discuss the——

Mr. **Early**. But you responded to my other question that everyone had to do it. NIH is the only one getting the cuts this year.

Mr. **Conte**. Would you yield a minute.

Mr. **Early**. Sure.

Mr. **Conte**. Yesterday you know, we asked that question and you answered that it is going to apply to everyone across the board.

But what Joe says is right. NIH is the only one that is implementing it in 1986, whereas all the other agencies, including defense, are going to implement it in 1987.

Is that right?

Mr. **Williams**. I do not believe that is exactly correct. We have savings built into the budget for 1987 reflecting implementation of this policy in 1987, and the circular does set a deadline, dropping from 26 percent down to 20 percent in April of 1987. That is later than we would like to see it start. Our budget assumes that the policy would be implemented earlier, and that is one of the comments we will make back to the Office of Management and Budget during the comment period.

Mr. **Conte**. Well, does Secretary Bowen have the discretion, as to when to implement the regulation for NIH and HHS?

Mr. **Williams**. Well, we could implement it earlier. April 1st, 1987 is when the circular requires that it be done. It could be done as early as April 1st, 1986.

Mr. **Conte**. You are going to implement in 1986; that is what you all say in here. You are going to do it in 1986.

Mr. **Williams**. The reduction from 26—our budget is from savings in 1987, from dropping from 26 percent down to 20 percent.

Mr. **Conte**. The 26 percent is already a reduction. It is currently about 33 percent, in some cases.

Mr. **Williams**. But the budget does not assume any particular—if I am correct—does not assume any particular budget savings this year from any implementation of that policy.

The savings are derived primarily from dropping the rate from 26 percent to 20 percent, and that would occur in 1987.

Mr. **Conte**. I have not got a straight answer yet.

Mr. **Early**. Your budget is complex and it is a big budget, but you are taking the sequestered money in NIH, and you are taking money out of the indirect costs to the universities. The Pentagon is not doing that. I mean, no other agency is doing it.

BUDGET REDUCTIONS

Mr. **Williams**. That is a different issue I think, how the reduction under Gramm-Rudman-Hollings will be achieved is a different issue than the Circular A-21 changes.

Mr. **Early**. Yes. Well, if you are supposed to be the director of an institute, or you are running a university, it all depends on whether you get the money or you do not get the money. And we are taking all of those cuts, Dr. Lenfant, and I think you are wrong.

Doctor, as bad as the specific cuts are, I sense, in my 12 years on this committee, that the flexibility or the autonomy of the directors is getting less and less.

Would you comment on that.

Dr. LENFANT. Well, yes, I would agree with that. We are receiving our apportionment broken down into a number of set categories, and Mr. Early, I am not arguing the bottom line of the budget but how it is broken down.

There is no question that it limits tremendously our flexibility to deal with needs and opportunities as they arise during the course of a year.

Mr. EARLY. And that is not progress, Dr. Lenfant, in my opinion. This morning, the Chairman was told that interferons are very productive, not as productive as we originally thought, but science came out and concluded with something else.

He also told us that the molecular cancer therapy for children was developed by a pediatrician. My goodness. And now we take away the autonomy from you people. That is not progress.

In my personal opinion, Doctor, NIH is going backwards as far as their specific direction in the last few years.

Dr. LENFANT. That is what I was saying a few minutes earlier. Being locked into numbers, and into budget categories, the result of the apportionment as it is done today, clearly prevents us from meeting some needs which we could take care of within any given appropriation.

Mr. EARLY. My personal observation, Doctor, is that the Directors at all the institutes, as much as I respect all of you, are not being independent anymore. You are letting OMB run your agency, which is disturbing.

Doctor, your institute always supported a number of clinical studies and trials. I thought that the Hypertension Detection and Follow-up Program, and the management of congenital vascular defects in new-borns were a tremendous success. Were they?

Dr. LENFANT. Yes.

CLINICAL TRIAL REDUCTIONS

Mr. EARLY. Do you have some ongoing clinical studies now?

Dr. LENFANT. Yes. We have in our books a number of clinical studies which are ongoing.

Mr. EARLY. Are you going to terminate any clinical studies?

Dr. LENFANT. Terminate? Probably not. But certainly we will have to reduce the scope of these studies and perhaps conduct them over a much longer period of time.

Mr. EARLY. Does the cost of the study vary from year to year for this reason?

Dr. LENFANT. Yes.

Mr. EARLY. Every year?

Dr. LENFANT. Well, you bring to attention an interesting situation. Clinical trials, like the ones you mentioned are conducted in two or three phases.

The first phase is the development, the design of the study. That is relatively inexpensive. And then you have the patient selection and recruitment phase that is often very expensive. It so happens that next year, many of our studies are entering the phase of patient recruitment, and that means that the costs will be very high next year.

Mr. EARLY. Doctor, do you plan to reprogram funds from other activities into these clinical studies or clinical trials?

Dr. LENFANT. That was my answer in response to the questions from the Chairman.

Mr. EARLY. But I want to get a specific answer. Do you have the flexibility to do that today?

Dr. LENFANT. At the present time, no, but I will certainly request reprogramming authority.

Mr. EARLY. As a Director, don't you think you should have the autonomy and the flexibility to do that? I mean, does Dr. Miller down at OMB have a better judgment of the Heart, Lung, and Blood Institute than you?

Dr. LENFANT. All I can say is that it would be very helpful to the Institute, and to our Advisory Council, which helps us to make the program decisions, if that flexibility existed within the Institute.

Mr. EARLY. Doctor, I have used my ten minutes but I have a lot more specific questions that I want to go into. Thank you.

Mr. NATCHER. Mr. Hoyer.

1987 BUDGET CUTS

Mr. HOYER. Thank you, Mr. Chairman. Doctor, I am not going to ask a lot of questions. One of the virtues of being at the end of the line here is that I get to read your statement. So that if you do not do your homework before you get here, you have got a lot of time to do it. I have read your statement, and, as always, with all of the directors of the various institutes, I find their statements very interesting, some of which I even understand.

It is a seven-page statement, and two lines deal with the budget. The last two lines.

"Mr. Chairman, the 1987 budget request for the National Heart, Lung and Blood Institute is $785,697,000."

I think Mr. Early's frustration is that the first six pages and 48 lines of the 50 lines, or twenty-five of the twenty-seven lines that are on that page, deal with, obviously, objectives that we think are critically important to the welfare of the country.

You have sustained approximately an 8 percent cut, 4.3 apparently under Gramm-Rudman-Hollings, and another 3.7 percent, as I figure it, in those ballpark figures.

All of the progress that Mr. Early, Mr. Natcher, and Mr. Conte and the others of us on this committee, thought we had made last year has been cut out and backed up.

I continually make the point that this Administration, in the fields of health, education, nutrition, sounds repeatedly the bugle call of retreat. Only in defense do we blow "charge." And that is I think unfortunate, and that is the frustration that Mr. Early, I think, reflects, and which Mr. Conte, Mr. Natcher, and I certainly share. I have got some questions here, but I am not going to ask them. This is not meant as any derogation of your posture, but they deal with some of the specifics that you have dealt with in the first six pages and twenty-five lines.

We are now getting, however, to the guts of it. I guess I will ask a question of mine, an historical question.

What can't you do, that you thought it in the best interest of the nation to do, in 1987, as a result of the budget cuts that have occurred?

If the President was sitting here, or "Cap" Weinberger was sitting here, they would not say you took an 8 percent cut. They would say you had taken at least a 12 percent cut because they would have added the 4 percent on to last year's figure, current services, and they would have said that you took a 12 percent cut.

My question is, what can't we do, that we ought to be doing, because of the budget priorities that have been submitted to us?

Dr. LENFANT. Well, as Mr. Early was pointing out, our Institute is concerned with a great number of high-priority items. Of the five main leading causes of death in this country, four are within the purview of our institute.

So, what I will say is that there are many projects that we can do with the appropriation or the budget that is proposed here, and we will do the best we can.

At the same time, there are a number of projects that are important, and will have to be put aside, because we know that we cannot complete these studies, in particular some of the clinical trial and population-based studies.

Mr. HOYER. Doctor, I appreciate that answer. According to my calculations if you had a current services budget your budget would be approximately 30 million dollars more.

What could be done if you had additional funds? If you can, Doctor—and you may not be able to do this—but if you can, if you could interpolate your budget as related to savings. A number of the directors of the institutes have given to us what I think is a very compelling figure, and that is, how much money in fact has been saved by the money that we have spent at NIH, in terms of continuing people in good health, maintaining them as taxpayers, and workers, and producers in our society. If you could do that—not now—but if you could do it, I think that is the kind of information we could use.

[The information follows:]

ECONOMIC SAVINGS TO SOCIETY FROM HEART, LUNG, AND BLOOD RESEARCH

Should additional funds become available, the Institute would provide additional support to research centers and research contracts, the mechanisms that support many of our clinical trials and population-based studies. Many of the clinical trials will result in applicable treatments having significant economic impact on health care costs. The Institute would also restore reductions to the intramural research program so that ongoing research projects can continue. Should sufficient funds become available, the Institute would propose less drastic negotiation levels in research project grants.

In assessing the economic savings to society that accrue from research supported by the National Heart, Lung, and Blood Institute it is not sufficient to consider the direct costs of diagnosis and treatment of individuals with disease. Of equal importance and even greater economic magnitude are the indirect costs that result from lost earnings owing to disability and, in the case of fatal diseases, to premature death. For example, in 1983, diseases of the cardiovascular system, lungs, and blood are estimated to have cost the nation a total of $133 billion, of which $58.7 billion were attributable to expenditures for diagnosis, treatment, and other direct costs of illness. The remaining $74.3 billion were indirect costs of which lost earnings due to premature deaths accounted for $47.8 bilion, and lost earnings due to disability were $26.5 billion. To put these figures in perspective, the total costs of illness due to diseases within the Institute's mandate constituted 23.8 percent of the nation's economic costs of illness in 1983.

Among the leading causes of death in the United States, heart disease is first; cerebrovascular disease, third; chronic obstructive pulmonary disease, fifth; and atherosclerosis, tenth. Hence, any research that reduces morbidity or mortality from diseases of the heart, lung or blood will have a significant economic impact. Although it cannot be quantified, it is reasonable to assume that the Hypertension Detection and Followup Program (HDFP) sponsored by the Institute served to reduce the costs of stroke and cardiovascular disease by establishing the effectiveness of systematic, sustained, antihypertensive therapy in reducing the morbidity and mortality from hypertension in people with "mild" hypertension--the most common form.

The Institute's Coronary Artery Surgery Study (CASS) showed that for patients with established coronary artery disease there was no difference in mortality between medical therapy and coronary bypass surgery. If this research leads to reduction in the number of surgical procedures, the savings in direct costs should approach $500 million per year. Indirect costs should also be reduced because patients treated medically rather than surgically lose fewer workdays because of disability.

Another clinical trial supported by the Institute demonstrated the efficacy of antenatal administration of steroids in preventing neonatal respiratory distress syndrome. The resulting economic savings for this therapy in pregnant women at high risk for newborns with respiratory distress syndrome should be about $300 million annually.

NHLBI-sponsored blood research has resulted in a new method for preparing blood for transfusion to patients with Cooley's Anemia or with other conditions that require lifelong transfusion therapy. The new technique results in red cells that are substantially less damaged that by previous techniques. Each transfusion lasts 50% longer and the patients require one-third fewer transfusions. Moreover, the new process is less expensive than the old. The annual direct costs saving is expected to be about $2,500 per patient.

Some studies still in the planning phase also hold promise of providing substantial economic savings. For instance, a planned study to determine whether percutaneous transluminal coronary angioplasty (PTCA) is a safe and effective therapy for certain types of patients with symptomatically severe multivessel coronary artery disease is expected to show that a substantial percentage of the over 200,000 bypass operations performed in the United States could be either deferred or rendered unnecessary. Since each bypass operation costs on the order of $20,000 for hospital expenses, while a PTCA procedure costs approximately $7,000, successful treatment of even 20% of the annual bypass case load could result in an immediate annual saving of over $500 million.

For more than a decade, chronic obstructive pulmonary disease (COPD) has been the most rapidly increasing major cause of death in the United States. Most of these patients have a long illness with progressive disability and multiple hospitalizations. The indirect costs due to incapacity substantially exceed the costs due to premature death. An NHLBI-sponsored trial is being undertaken, designed to determine whether early intervention in smokers with early evidence of airway obstruction can alter the course of disease development. Because 10 million people in the United States already suffer from COPD, progress in retarding the disease could result in sizeable savings in both direct and indirect costs of illness.

SAVINGS IN HEALTH CARE BENEFITS

Mr. HOYER. Your statement is excellent, as it always is, and I have only been here a short period of time as compared to everybody but Barnie Dwyer on this committee. Barnie and I are so "wet behind the ears" compared to Mr. Early, and Mr. Early is junior to the folks to his right.

But I think that this is the kind of information that we need to make a considered responsible judgment on behalf of the American people as to where they want to put their dollars.

Dr. LENFANT. It is interesting that you put it this way, Mr. Hoyer. Yesterday, when Dr. Wyngaarden made his opening statement to you, if my memory does not fail me, he said that one of the fruits of the research conducted by NIH was a cost savings in the health care system of about $2.5 billion.

Mr. HOYER. Two and a half billion was in the statement yesterday.

Dr. LENFANT. That is correct, and he referred to twelve items, although in his statement, he specifically mentioned only three studies.

Mr. HOYER. Yes.

Dr. LENFANT. I was very pleased to see that two of the three are coming from our Institute. One is the Coronary Artery Surgery Study which led to a savings of $500 million a year, and the other one resulted in the substitution of a medical treatment to a surgical treatment of a congenital defect, which led to a savings of about $200 million a year.

So, out of these three examples which were reported yesterday, we would take credit for a savings of about $700 million per year.

And I believe that, indeed, there are many research activities, that are bringing about some substantial savings in our health care system.

Mr. HOYER. I appreciate that, and if you could sort of flesh that out as it relates to your institute. I think I have probably asked that question of the other institutes as well. I am relatively confident that the three gentlemen to my right, with the help of the fourth sitting there, not looking at me—the other three are looking at me at least—are going to tell me that I am not supposed to allow this to happen, they are not going to allow it to happen, so I feel comfortable about that. Thank you, Mr. Chairman.

APPROPRIATION ACT AMENDMENT

Mr. NATCHER. Dr. enfant, as you know, the President has requested language which would amend section 202 of the 1986 appropriation act by striking out "no fewer than 6,100 new and competing projects" and inserting, in lieu thereof, "the maximum number of new and competing projects as the Secretary of Health and Human Services determines, in light of appropriations available for fiscal year 1986, would maximize scientific progress and enhance stabilization of the science base."

Now, Dr. Lenfant, if we approve this language, can you tell us how many projects would be funded by your institute in 1986?

Dr. LENFANT. It would be 817 new or competing——

Mr. NATCHER. 817?

Dr. LENFANT. 817, sir.

Mr. NATCHER. How many projects would be funded if Congress approves the proposed language change but does not approve the proposed rescission of $11,469,000?

Dr. LENFANT. 886.

Mr. NATCHER. Thank you. Now under "Other Research Mechanisms," in your statement, you tell us that in addition to investigator-initiated research, "it is also important, however, to continue to identify other avenues of research, particularly clinical validation and technology transfers, such as our centers programs and clinical trials."

Does this statement mean, Dr. Lenfant, that we are placing too much emphasis on research project grants at the expense of clinical trials and research centers?

Dr. LENFANT. No, it does not mean that. As I pointed out to you at the beginning, Mr. Chairman, our Institute has a great number of programs that cannot be supported by the same mechanisms of support, and we have a great deal of reliance on mechanisms of support other than the research grants, such as the research centers and the activities which are supported by contracts, such as clinical trials and population-based studies.

Mr. NATCHER. If you would insert in the record a list of the clinical trials being supported in 1985 and 1986, and those planned for 1987.

[The information follows:]

CLINICAL TRIALS IN 1985–87

	Continuing in fiscal year—	
	1986	1987
Ongoing trials in fiscal year 1985:		
Lipid research clinics and coronary primary prevention trial [1]	Yes	Yes
Multicenter investigation of limitation of infarct size [1]	No	No
Thrombolysis in myocardial infarction	Yes	Yes
Coronary artery surgery study [1]	Yes	Yes
Studies of left ventricular dysfunction	Yes	Yes
Cardiac arrhythmia pilot study	Yes	Yes
Systolic hypertension in the elderly program	Yes	Yes
Percutaneous transluminary coronary angioplasty registry	Yes	Yes
Diagnosis of pulmonary embolism trial	Yes	Yes
High frequency intervention for neonatal respiratory distress	Yes	Yes
Chronic obstructive pulmonary disease	Yes	Yes
Clinical course of sickle cell disease	Yes	Yes
New trials in fiscal year 1986 after sequestration:		
Cardiac arrhythmia treatment study.		
Trials of hypertension prevention.		
New trials under the 1987 President's budget: None.		

[1] Primary results reported; only further data analyses or late followup.

Mr. NATCHER. Also, if you would, insert a list of the clinical trials which would be supported in 1987 if additional funds become available.

[The information follows:]

NEW CLINICAL TRIALS IN 1987 IF ADDITIONAL FUNDS WERE AVAILABLE

Proposed trial	Number of years	First year cost	Total cost
Bypass angioplasty revascularization investigation	8	$1,000,000	$28,600,000
Dietary intervention in children with elevated low density lipoprotein levels	7	700,000	9,255,000
Treatment of pulmonary embolism with thrombolytic agents	5	1,000,000	10,000,000
Continuous positive airway pressure for treatment of sleep apnea	6	800,000	4,000,000
Penicillin prophylaxis in sickle cell disease	2	900,000	1,800,000
Natural history of posttransfusion NANB hepatitis	4	1,000,000	3,215,000
Deep vein thrombosis diagnosis and treatment	5	600,000	10,800,000
Post coronary artery bypass graft program	5	850,000	29,500,000
Postmenopausal estrogen use and coronary heart disease risk	3	4,000,000	12,700,000

RESEARCH CENTERS

Mr. NATCHER. Dr. Lenfant, what are your current plans for support of research centers in 1986 and 1987?

Dr. LENFANT. In 1985, our Institute committed $84.6 million for the support of 60 centers. The appropriated amount for 1986 was $86.5 million, but with sequestration and rescission, the amount in the budget, at this time, is $82.8 million.

For 1987, it is projected to be $75.8 million. As I mentioned, Mr. Chairman, the Institute supports 60 centers, 10 of which are mandated by Congress. These are centers for sickle cell disease research.

The 50 other centers are divided among all of our programs in the heart, lung and blood areas. Next year, out of these 50 centers, 24 are up for renewal.

The renewal applications have been submitted and are currently under review, and I am told by my staff that the research activities which are proposed are innovative, imaginative, and most likely will bring about some substantial new information.

Next year we will clearly have some difficult decisions to make in funding this wave of new activities proposed by the centers that are up for renewal, given the amount that we will have to spend for the centers.

Mr. NATCHER. Now if you will, insert in the record at this point a list of the research centers supported in 1985 and 1986, along with your plans for 1987, and include the amount of the grants to each one. If you would place that in the record for us.

[The information follows:]

RESEARCH CENTERS FOR 1985, 1986, 1987

In FY 1986 and FY 1987, the Institute plans to fund 60 research centers, the same number supported in FY 1985. The amounts required to provide estimated full costs for these centers are $87,409,000 in FY 1986 and $90,383,000 in FY 1987.

The NHLBI funded the following research centers in FY 1985:

Arteriosclerosis SCORs*	FY 1985 Funding
Baylor College of Medicine, Houston, Texas	$1,885,660
Columbia University, New York, New York	2,092,037
Louisiana State University, Baton Rouge, Louisiana	2,691,382
University of California, San Diego, California	1,521,326
University of California, San Francisco, California	1,897,765
University of Chicago, Chicago, Illinois	2,606,002
University of Iowa, Iowa City, Iowa	2,054,250
Wake Forest University, Winston-Salem, North Carolina	2,649,443
Subtotal	17,397,865
Hypertension SCORs*	
Boston University, Boston, Massachusetts	1,961,621
Cleveland Clinic Foundation, Cleveland, Ohio	864,976
Cornell University, New York, New York	2,394,705
University of Alabama, Birmingham, Alabama	1,060,265
University of California, San Diego, California	1,089,142
Vanderbilt University, Nashville, Tennessee	1,706,441
Subtotal	9,077,150
Ischemic Heart Disease SCORs*	
Cedars-Sinai Medical Center, Los Angeles, California	1,396,920
Duke University, Durham, North Carolina	1,933,901
Harvard University, Boston, Massachusetts	2,270,945
Johns Hopkins University, Baltimore, Maryland	1,400,156
University of Alabama, Birmingham, Alabama	1,174,603
University of California, San Diego, California	1,614,649
University of Iowa, Iowa City, Iowa	943,366
University of Texas, Dallas, Texas	1,702,759
Washington University, St. Louis, Missouri	3,642,460
Subtotal	16,079,759
Pediatric Pulmonary Diseases SCORs*	
Brigham and Women's Hospital, Boston, Massachusetts	941,524
Columbia University, New York, New York	1,372,764
University of California, San Fransisco, California	565,836
University of Minnesota, Minneapolis-St. Paul, Minn.	627,382
Univ. of North Carolina, Chapel Hill, North Carolina	1,031,449
University of Washington, Seattle, Washington	660,829
University of Wisconsin, Madison, Wisconsin	644,776
Vanderbilt University, Nashville, Tennessee	1,126,245
Subtotal	6,970,805

Occupational & Immunologic Lung Diseases SCORs*	FY 1985 Funding
National Jewish Hosp. and Res. Ctr., Denver, Colorado	843,075
Tulane University, New Orleans, Louisiana	1,510,456
University of Vermont, Burlington, Vermont	1,336,490
Subtotal	3,690,021
Adult Respiratory Failure SCORs*	
Massachusetts General Hospital, Boston, Massachusetts	911,701
St. Louis University, St. Louis, Missouri	614,048
University of California, San Diego, California	596,855
University of Texas, San Antonio, Texas	1,019,906
University of Washington, Seattle, Washington	955,648
Subtotal	4,098,158
Pulmonary Vascular Diseases SCORs*	
Children's Hopital, Boston, Massachusetts	615,964
University of California, San Francisco, California	553,901
Vanderbilt University, Nashville, Tennessee	1,372,774
Subtotal	2,542,639
Chronic Airways Diseases SCORs*	
Harvard University, Boston, Massachusetts	1,117,684
University of Arizona, Tucson, Arizona	1,493,705
Subtotal	2,611,389
Sickle Cell Centers	
Boston City Hospital, Boston, Massachusetts	951,704
Children's Hospital Medical Center, Cincinnati, Ohio	1,295,247
Columbia University, New York, New York	1,830,078
Duke University, Durham, North Carolina	704,282
Howard University College of Medicine, Washington, D.C.	1,983,343
Medical College of Georgia, Augusta, Georgia	1,363,509
University of California, San Francisco, California	1,285,415
University of Illinois, Chicago, Illinois	1,865,151
University of Southern California, Los Angeles, Calif.	1,461,786
Wayne State University, Detroit, Michigan	1,334,678
Subtotal	14,075,193
Thrombosis SCORs*	
Cornell University Medical Center, New York, New York	2,181,476
Temple University, Philadelphia, Pennsylvania	2,586,305
Univ. of North Carolina, Chapel Hill, North Carolina	944,248
Washington University, St. Louis, Missouri	613,953
Subtotal	6,325,982
Transfusion Medicine SCORs*	
Center for Blood Research Inc., Boston, Massachusetts	673,364
Stanford University, Stanford, California	1,079,777
Subtotal	1,753,141
Total Research Centers, FY 1985	84,622,102

*SCORs (Specialized Centers of Research)

AUTHORIZING LEGISLATION

Mr. **Natcher**. Dr. Lenfant, Congress recently extended, as you know, your authorizing legislation by overriding a veto. How does this new legislation affect your programs, generally?

Dr. **Lenfant**. We believe, and our Advisory Council believes that this authorizing legislation is extremely supportive of our programs, and I cannot think of anything negative to say about it.

Mr. **Natcher**. If you will insert in the record at this point a summary of the provisions of the new law as they affect your Institute, if any.

[The information follows:]

Effects of New Legislation

The "Health Research Act of 1985", P.L. 99-158, does not substantially change the previous authorizing legislation for the National Heart, Lung, and Blood Institute. Certain specific areas will have a positive impact by allowing increased flexibility and broader discretion for the Director of the Institute. These are: (1) the ability of the Director, NHLBI to fund direct costs for grants or cooperative agreements of less than $50,000 without approval of the National Heart, Lung, and Blood Advisory Council (previous limitation was $35,000); and, (2) the deletion of the $5 million limitation on payments to any center.

AIDS RESEARCH

Mr. **Natcher**. Now, under AIDS, how much did you spend on AIDS research in 1985, and how much do you expect to spend in 1986 and 1987?

Dr. **Lenfant**. In 1985, we spent $9.3 million for AIDS research. In 1986, we had projected $11.2 million, but this activity, like all activities, was cut by 4.3 percent, and that brings it to $10,718,000 for 1986.

Our projection for 1987 is $17,091,000. These funds, however, will be placed in the Office of the Assistant Secretary for Health, and presumably will be redistributed to the Institute.

Mr. **Natcher**. At this point in the record, just place a short summary in there, if you will, Dr. Lenfant, concerning the types of AIDS research being conducted by your Institute, just a little short statement.

[The information follows:]

AIDS Research

As part of its mandate to support research to improve the safety of the blood supply, the National Heart, Lung, and Blood Institute (NHLBI) fosters development of blood tests to control the spread of infection, explores methods to inactivate infectious agents present in blood or blood products, and supports the development of globulin preparations which may be useful in controlling the spread of infection from blood tranfusion.

The NHLBI is in the second year of a grant program to develop tests for AIDS carriers. An ELISA test using a chemically synthesized peptide, identical to part of the coat of HTLV-III, is under development and may lead to a more specific assay than current tests for antibody to HLTV-III; this same peptide is also an exciting candidate for a vaccine. The Institute recently released a solicitation encouraging research to develop and evaluate procedures that could be utilized in screening and monitoring the infectivity of individuals infected with HTLV-III, such as improved assays to detect and/or confirm the presence of antibody and techniques for the identification of the virus or its components.

In 1985, the Institute awarded a contract to develop an immune globulin to the AIDS virus. Early results indicate that virus-neutralizing factions can be found and offer hope that such a preparation could provide passive immunization to exposed individuals.

Animal models for AIDS are essential for assessing the clinical course of the disease, for determining safety and efficacy of therapeutic agents, for studying vaccine candidates and for confirming viral inactivation in blood products. The Institute supports the study that first documented clinical evidence of transmission of AIDS from a human to a chimpanzee. This project recently showed transmission of the virus from chimpanzee to chimpanzee and will examine factors that contribute to the clinical expression of HTLV-III infection.

In FY 1984, the NHLBI initiated a five year, multi-center prospective study to evaluate the effects of transfusion of blood and blood products on the immune system of recipients and to determine the relationship of these effects to viral infections, especially HTLV-III. Two groups of transfusion recipients are being enrolled: (1) medical and surgical patients who received transfusions before HTLV-III antibody screening was instituted but whose transfused sample is now know to contain antibody; and (2) persons with congenital hematologic disorders that require frequent transfusions, including hemophilia, sickle cell disease and Cooley's anemia. This program will answer questions about the transmission of the AIDS virus by blood transfusion and the risk for further transmission, primarily among family members, from those who acquire the virus in this way.

The Institute plans to study the effectiveness of current screening procedures. A negative test for HTLV-III antibody does not absolutely assure that the donor is free of virus. Instances of antibody negativity or variable positivity in infected persons have been dwecribed. A study to determine the magnitude of this potential problem is now being designed for implementation in FY 1987.

The Institute also supports a variety of investigator-initiated activities, including a grant to the New York Blood Center to evaluate the most effective counselling techniques for blood donors who are identified as HTLV-III antibody positive by current testing procedures.

NHLBI funding for AIDS research was $9,323,000 in FY 1985. Estimates for FY 1986 and FY 1987 are $10,718,000 and $17,091,000, respectively.

CHOLESTEROL

Mr. NATCHER. Tell us about the latest research results relating to the health effect of cholesterol. What would you say, Doctor?

Dr. LENFANT. Well, the evidence in hand clearly demonstrates in a definitive way, that high blood cholesterol increases markedly the risk of coronary heart disease.

It is interesting that approximately 50 percent of the heart attacks in this country are to be found in the 20 percent of the population that have a cholesterol level considered to be a high risk.

Further, some studies have demonstrated that by reducing the cholesterol in the blood by approximately 1 percent, it causes a decrease risk of heart attack of approximately 2 percent.

So the evidence, at this point in time, is really not questionable.

Mr. NATCHER. Doctor, what advice does your Institute give to the public regarding the consumption of red meat, eggs, and dairy products?

Dr. LENFANT. Our recommendations to the public are not to eliminate these food products from their consumption, but to limit this consumption. For instance, we do recommend that the consumption of cholesterol should not exceed 270 or 280 milligrams per day. And the consumption of saturated fat, which is mostly found in animal fat, should not exceed 10 percent of the fat consumption. We also recommend that total fat consumption should not exceed 30 percent of the caloric input for any individual.

I should tell you, Mr. Chairman, that during the last 18 months, or so, we have had many discussions, and I personally have had many discussions with representatives of the meat industry and of the egg industry, specifically with their trade groups, such as the United Egg Producers of America and the Cattlemen's Association. It is interesting that these two groups are completely supporting the recommendations that we make in our educational programs.

Last year, when the Egg Producers of America met for their yearly convention in New Orleans, they had a stand in their exhibit hall where people could come and have their blood cholesterol measured, and some of my staff were there to give information and help.

We feel very strongly, that if our cholesterol education program is to be successful, it must have the broad support of the entire community, and we feel confident that if the Egg Producers of America, and the Cattlemen's Association support our program, we are in good shape.

HEART TRANSPLANTS AND ARTIFICIAL HEART

Mr. NATCHER. Now, Doctor, bring us up to date, briefly, if you will, on the current status of artificial heart implantations as well as heart transplants.

Where are we now, Doctor?

Dr. LENFANT. Since we last met, Mr. Chairman, artificial hearts, or like devices, have been implanted in 29 patients. Five of these 29 patients have received an artificial heart as a total replacement. By total replacement, I refer to cases similar to those of Mr. Hayden and Mr. Schroeder, whom we hear about in the news.

Twenty-four other patients have received an artificial heart, or like device, for what is called a bridge of transplants. That is, these people received an artificial device in order to wait for the availability of a donated human heart. Of these 24 patients who received a device as a bridge to transplants, 15 are still surviving and 4 of these 15 are still waiting for a heart to be donated.

A few weeks ago I testified to the House Committee on Science and Technology, the Subcommittee on Investigation and Oversight. The issue of the artificial heart was discussed at great length. Most people who testified expressed a great deal of support for the bridge to transplants use of the artificial heart.

Your other question was about the transplants. During the last year, we have seen a tremendous increase in the number of heart transplants performed, in the United States, and in the whole world, as well.

In 1984, 358 heart transplants were done in the United States and 606 throughout the world. Last year, these numbers, respectively, were 633 and 1,028, almost double what we had seen the year before.

I believe that this must be a result of a greater awareness and consciousness of the public toward heart and other organ donations.

CONSTRUCTION FUNDS

Mr. NATCHER. Dr. Lenfant, you are requesting no funds for construction I believe in 1987. If you had additional funds, would you award some grants for construction?

Dr. **Lenfant**. Yes, sir.

Mr. **Natcher**. How serious is the need for construction of research facilities for research supported by your institute?

Dr. **Lenfant**. It is a very significant and important need. As we come here each year, we speak about all the new technologies—molecular biology, cell biology, genetics and biochemistry now utilized by researchers in all fields of medicine including the cardiovascular, the pulmonary, and the blood areas. The introduction of these technologies is relatively new, and the facilities to use them do not exist. This is the reason why, when a few years ago, Congress first gave us construction money, we specified that these monies should be used for the development of facilities which would enable these technologies to be used.

Mr. **Natcher**. Doctor, do you have a backlog of unfunded requests for construction funds?

Do you have any kind of a backlog, and how large is it, if so?

Dr. **Lenfant**. Yes, we do. A number of applications from last year's competition are in-house and constitute a backlog.

NOBEL LAUREATES

Mr. **Natcher**. I believe two winners of the 1985 Nobel Prize for Medicine have been primarily supported by grant funds from your Institute. If you would, now, Doctor, describe, just briefly, the work for which the Nobel Prize was awarded to Dr. Brown and Dr. Goldstein.

Dr. **Lenfant**. That research is a long series, of approximately ten years of very fundamental studies on the metabolism of blood cholesterol. In performing these studies Dr. Brown and Dr. Goldstein discovered the existence of receptors. These receptors are structures found on the surface of cells, particularly in the liver. These receptors have the ability to absorb the bad cholesterol, and remove it from the blood.

The importance of this research is considerable in many respects, especially with regard to the metabolism of cholesterol and the treatment of excess cholesterol. This condition often results from a genetic disorder, but there is also a "garden variety" of hypercholesterolemia that affects millions of people in this country.

In addition to impacting these pathological entities, the same principle can now be applied to other metabolic disorders, and basically it has provided the scientific community with a paradigm for research, which can be utilized and replicated for several disease categories.

Mr. **Natcher**. Doctor, were they all supported by investigator-initiated research grants, both of these two gentlemen?

Dr. **Lenfant**. Yes, sir. When Dr. Brown and Dr. Goldstein began their research in the early 1970's, they were supported mostly by the National Institute of General Medical Sciences. As their research focused more and more on cholesterol, their grant applications, which at that time were individual research grants, were assigned to our Institute, and for the last eight years, they have been supported by what we call program project grants, which are large research grants encompassing a number of such projects.

The amount that has been funded by our Institute to these investigators during the last 15 years is approximately $7.5 million, and prior to that, they had received approximately $500,000 from the National Institute of General Medical Sciences.

Although this research has cost the American people approximately $8 million, the impact of that research is clearly worth many times this amount of money, and this is why it was recognized by the Nobel Prize, and the Lasker Award given last year.

Mr. **Natcher**. Thank you, Dr. Lenfant. Mr. Conte, do you have any additional questions?

ARTIFICIAL HEART

Mr. **Conte**. Doctor, the Chairman was asking some questions about artificial hearts, and every year you bring us up to date, and you bring us a new heart up here to look at. We had the Phoenix heart and the Jarvik heart. Have you got anything in your bag today?

Dr. **Lenfant**. Yes, I do have something in my bag today, but it is not an artificial heart. It is another piece of equipment that is related to the heart and its value is that it helps the natural heart to keep on functioning as it should, for a long period of time.

Let me tell you about it. Some patients, for a variety of reasons develop irregularity in their heart beats. The heart beats can become so abnormal, that the function of their heart is no longer satisfactory. It may be that if no treatment is given, these persons would die from an extreme form of the disorder called fibrillation.

This device is implanted in the chests of patients who have severe heart beat disorders. The device recognizes when the heart beat becomes irregular, or when there is fibrillation, it then sends an electrical shock which returns the heart beat to normal.

This device was first developed about 5 or 6 years ago. The first one was implanted in 1980. Today, about 600 have been implanted. Last October the device was approved by the Food and Drug Administration and I expect that many more are going to be implanted from now on.

Our Institute supported the basic research leading to the concept of the development of this equipment. From that basic research, private industry developed the device. Then in one of our centers of research we have done all the clinical studies that eventually led to the FDA approval of the device.

Let me add that before we had this device, about 50 to 60 percent of patients with severe heart beat irregularities would die. Of those who have been implanted, the survival rate is about 85 percent. So the mortality went from 50 to 60 percent, to approximately 15 percent. So here is a device that is going to have a tremendous impact.

Mr. **Conte**. Is there a battery in there?

Dr. **Lenfant**. Yes. It is a self-contained device.

Mr. **Conte**. Is it a life-long battery, or do you have to change it?

Dr. **Lenfant**. No, it lasts several years, depending on how frequently it sends an elecrical shock.

Mr. **Conte**. The whole thing is implanted in the body?

Dr. **Lenfant**. Yes. If you want to see it; you might be interested.

Mr. **Conte**. How does that differ from a pacemaker?

Dr. **Lenfant**. A pacemaker sends stimulation to the heart continuously to make it beat at the speed that it should.

What the pacemaker does not recognize, is if the beat becomes irregular. Unlike the pacemaker, the device we have here replaces the physician, in his absence, because it is going to recognize when there is something abnormal going on, and it will send an electrical shock to correct the irregularity.

CLINICAL TRIALS

Mr. **Conte**. Doctor, is there any money in your fiscal year 1986 or 1987 budget for the clinical trial of TPA, a drug which you have testified here dissolves blood clots while they are causing heart attacks?

I read an article in yesterday's "Wall Street Journal" that NHLBI will not go through the second phase of the trial because the drug has been so successful. Is that so?

Dr. **Lenfant**. Well, there are 2 answers to your question.

Mr. **Conte**. Right. There are two.

Dr. **Lenfant**. The statement made in the "Wall Street Journal" was not entirely correct. The first phase of the clinical trial to assess the efficacy of the drug has been completed, and has proven the drug to be very successful. Therefore there is no need to continue with the same protocol.

However, as I mentioned in my opening remark, what the drug does is dissolve blood clots in the artery, but it does not correct whatever the abnormality is in the artery that has caused the blood to clot.

And so the question today is to determine whether there is a need for another co-primary treatment, meaning should you do something else at the same time as you inject the drug to treat or eliminate what has been stimulus for the blood clot to form?

As I mentioned earlier, the stimulus for the blood clot to form is often the narrowing of the artery. So what is proposed to be done is to insert the balloon tipped catheter and inflate the balloon in order to eliminate the narrowing of the artery where the blood clot formed.

This is what we want to study now on a large number of patients, and is a very high-priority item in our program.

We are evaluating at the present time, how quickly we are going to be able to begin this study, one that we feel is very important. This study has the potential to benefit a large proportion of the 700,000 people who get a heart attack each year. The drug treatment can be given very quickly. In fact, recently I saw in the "New York Times", an article about a helicopter that was dispatched to pick up a person who had a heart attack, and the medic on the helicopter injected this drug. Upon arriving at the hospital, the patient was in fairly good condition, meaning the seriousness of the heart attack had been removed, so to speak, by the injection of the drug.

But again, although we can remove the blood clot, that does not mean that the stimulus for the formation of the blood clot is gone, and that is what we need to address today.

Mr. CONTE. Why not just go in there and have a bypass?

Dr. LENFANT. Well, first of all, a bypass is a complex surgical procedure that you cannot do everywhere.

If the procedure I am talking about works——

Mr. CONTE. You could do it in an office?

Dr. LENFANT. Well, perhaps not in the office but certainly in facilities which are not as sophisticated as what you need for cardiac surgery for a bypass.

In addition, a bypass is a very expensive procedure. Today, a bypass is probably on the order of $30,000. The procedure that I am talking about is probably less than $10,000.

Mr. CONTE. Thirty thousand for a single bypass. What if you have a triple? Do they give you a bargain basement price?

Dr. LENFANT. Well, maybe there is a discount, I do not know.

Mr. CONTE. I still swear that I read about this other technique I was talking about earlier. I read about the balloon and all, but I read about this other thing that is put in with a catheter.

And it has got a blade on it and it just cuts the layers away. I am going to find it and I will show it to you.

I think that it was discovered in a VA hospital.

Dr. LENFANT. Please do.

Mr. CONTE. Doctor, in clinical trials, are there any ongoing clinical trials that are threatened by the Gramm-Rudman-Hollings or the rescission requests in Fiscal Year 1986 or by the budget requests of Fiscal Year 1987?

Dr. LENFANT. Yes, Mr. Conte. Excuse me, you said 1986 or 1987?

Mr. CONTE. 1986 or by the budget requests for 1987.

Dr. LENFANT. In 1986, we had planned to have three clinical trials and, in fact, only two will be initiated at a slower pace in 1986. And in 1987 none of our proposed clinical trials will begin.

RESEARCH CENTERS

Mr. CONTE. Okay, you remember, Doctor, last year when we got all tied up by the OMB Directive to limit the number of grants in centers by a back-door forward-funding mechanism. And the funding of two hypertension centers was in question. Could you tell us what happened to your ability to fund those two centers?

Dr. LENFANT. We funded them at the end of the year. Dr. Wyngaarden allocated one more center to us and so last year we funded three new centers instead of two as we had discussed when I testified to you last year.

Mr. CONTE. There is also an issue of whether you would be able to initiate a transfusion center program. What happened to that?

Dr. LENFANT. We did initiate our transfusion medicine center program and all three centers that I talked about were allocated to this particular area.

Mr. CONTE. I have used my ten minutes, Mr. Chairman.

Mr. NATCHER. Mr. Stokes.

SICKLE CELL ANEMIA

Mr. STOKES. Thank you, Mr. Chairman.

Doctor Lenfant, are we making any progress or any advances in terms of the diagnosis and treatment for sickle cell anemia?

Dr. **Lenfant**. Yes. In fact, with regard to diagnosis two important things have occurred. One during the last few years and one which is emerging now, within our own laboratories at NIH.

One is the prenatal diagnostic test which now can be done very simply and inexpensively. All experts in the field advocate that it be done routinely in the population at risk. Unfortunately at the present time, this is not routinely being done.

The second thing that is emerging in our laboratories is concerned with one of the serious complications of sickle cell disease known as aplastic anemia, a condition where the bone marrow all of a sudden stops producing new red cells. Some work being done in our laboratory seems to incriminate a virus that is responsible for this bone marrow depression. Of course, this research is extremely important and it is actively pursued in our laboratory.

Now, with regard to treatment, one of the main complications of sickle cell disease is the risk of infection, pulmonary infection and sometimes septicemia, in infants. What we have done this year, was to complete a most valuable clinical study on prophylactic penicillin for use in infants. And we have demonstrated that with this treatment we can reduce by approximately 85 percent the incidence of pulmonary infection and septicemia. This is a major advancement in the treatment of infants or the care of infants with sickle cell disease.

SICKLE CELL RESEARCH CENTERS

Mr. **Stokes**. Doctor, ten comprehensive sickle cell research centers were supported in 1985 at a total cost of $15.1 million. How many such centers will be supported in 1986 and in 1987 and in what amounts?

Dr. **Lenfant**. In 1986 the amounts will be approximately $11.5 million and it is anticipated that in 1987, it will be on the order of $12 to $13 million. This is what we need to fund them.

However, Mr. Stokes, as we discussed earlier, when you were out of the room, we have a problem in 1987. And frankly, at this point in time, I cannot tell you how this problem will be resolved.

Incidentally, you may know that these sickle cell centers will be up for renewal in 1988.

SICKLE CELL DIAGNOSTIC TECHNIQUES

Mr. **Stokes**. According to your budget justification, pilot projects are needed to study the usefulness of new technologies, such as magnetic resonance imaging in the diagnosis of sickle cell anemia. What do you have in mind there, Doctor?

Dr. **Lenfant**. Magnetic resonance is an imaging technique that is very interesting. It could be used to measure blood flow in patients with sickle cells, especially in very small vessels. Today, it is not possible to make these measurements. We have described in the justification an approach to investigate the usefulness of this new non-invasive technique.

Mr. **Stokes**. Are you planning to fund these pilot projects out of the sickle cell anemia research centers budget, or in addition to them?

Dr. **Lenfant**. The plans were to fund them. However, at the present time, this activity has been postponed.

MINORITY INITIATIVES

Mr. **Stokes**. Can you give me an update on the four minority initiatives: the minority school faculty development awards, the minority institution research training program, and the visiting professor program for minority institutions and the research fellow program for investigators at minority institutions?

Dr. **Lenfant**. Yes, sir. These are four programs that we initiated last year to enhance the research capability and research training in minority health profession schools.

All of the programs have been initiated, but the only one which really has begun, that is, where we have made some awards, is the Minority School Faculty Development Program. This is a program for minority faculty to go to a majority school for, usually, a five year period of time. Last year we made five awards and we anticipate to make four more this year.

Mr. **Stokes**. Now, I notice that $405,000 was allocated for these activities in fiscal year 1985. Why such a small amount?

Dr. **Lenfant**. Because the five programs awarded were the only ones received that were found to be meritorious. These are fairly competitive programs.

Mr. **Stokes**. Mr. Early.

1987 PAYLINE

Mr. **Early**. Thank you, Mr. Stokes.

Dr. Lenfant, what payline will you fund under the 1987 budget request?

Dr. **Lenfant**. The official projected payline is 186 for the 1986 appropriation level.

Mr. **Early**. What was your payline in 1985?

Dr. **Lenfant**. 177.

Mr. **Early**. What was it in 1986, without the rescission?

Dr. **Lenfant**. It would also be 186.

Mr. **Early**. What percentage of approved grants were funded—

Dr. **Lenfant**. Excuse me, Mr. Early, I did not correctly answer your question. With sequestration and rescission it would be 179. Without rescission, it would be 186.

Mr. **Early**. And this budget is going to fund that 186?

Dr. **Lenfant**. That is the official payline.

Mr. **Early**. That does not work out with me.

Dr. **Lenfant**. For 1987, it is officially projected to be 175. But I believe it will be significantly reduced.

Mr. **Early**. Oh, I thought that you had told me 186.

What percentage of approved grants would be funded under the 1987 budget request?

Dr. **Lenfant**. Approximately 29 percent.

Mr. **Early**. What percentage were funded in 1985?

Dr. **Lenfant**. Approximately 36.8 percent.

Mr. **Early**. 36.8 percent and it went down to 29 percent. Doctor, have we got a revolution? Doctor, the justification states that there will be a downward negotiation of almost 16 percent in competing grants and almost 10 percent in non-competing grants, is that true?

Dr. **Lenfant**. Yes, sir.

1987 BUDGET REDUCTIONS

Mr. **Early**. Will that be averaged out or will you have some choice in what the reduction will be?

Dr. **Lenfant**. We do have that choice, but when it comes to negotiating an average of 17.6 percent, one hesitates to impose an additional cut.

So although we do have the flexibility——

Mr. **Early**. There is no flexibility there, Doctor, with a 16 percent decrease. There is no money. My gosh, to make that type of a reduction.

INDIRECT COST CAP

With the Chairman's indulgence, I would like to ask Mr. Williams a question. In the February 12, Federal Register, there was a proposal concerning indirect costs, and the subparagraphs were identified as A through F. Subparagraph B dealt with capping the costs at 26 percent in 1986, and then subparagraph C dealt with reducing it to 20 percent in 1987. Subparagraph D said that the implementation date could be deferred without authorization.

Now, I was saying to you, Mr. Williams, what cuts do you have in your budget that are associated with the indirect costs in 1986?

Or maybe Dr. Wyngaarden can help.

Mr. **Williams**. I think that the 26 percent represents what is currently being paid to the extent that it is being capped, it has no budget affect and we have not included—no budget savings are reflected in the budget.

Mr. **Early**. You are not taking any reductions in 1986 for indirect costs?

Mr. **Williams**. That is right. In 1987, we are taking savings, but in NIH about $85 million. That reflects the reduction from 26 to 20.

Mr. **Early**. Again, I know how complex that budget is, but those numbers are not in line with what I thought.

Do you agree with that. Dr. Wyngaarden?

Dr. **Wyngaarden**. Those are the figures that we have——

Mr. **Early**. The Federal Register says that the cuts will be a $100 million in 1987; and $200 million in 1988 but my institutions say they have gotten cut this year.

Dr. Lenfant, do you have anything to do with that?

The indirect cost factor, the A-21 circular?

Dr. **Lenfant**. No, I do not have anything to do with that.

Dr. **Wyngaarden**. Mr. Early, your confusion may be the different dates and Mr. Williams can explain that. I think that there is some confusion about the public dates, that the budget as submitted does not reflect the dates in the Federal Register Notice.

Mr. **Early**. Okay, Mr. Williams, I suggested that other agencies were not taking the cuts in 1986 and you, I think, answered that NIH is not alone. I wish that you would check it.

Mr. **Williams**. I will do that.

NEW TECHNIQUES IN THE TREATMENT OF HEART ATTACKS

Mr. **Early**. Dr. Lenfant, in the past you have described a new drug that dissolves blood clots like those that cause heart attacks. What is the status of this work? Is the treatment ready for routine practice or is there further work that must be done before physicians can use it?

Dr. **Lenfant**. We know that the drug does dissolve the blood clots. There are some questions to be answered which are left before it can be used routinely. Namely, what happens to the stimlus in the artery, or the lesion, you might say, in the artery that is responsible for the formation of the clot in the first place?

Mr. **Early**. Doctor, I understand that that particular test is being combined with the balloon dilation of narrow coronary arteries. How many people can benefit from this approach?

Dr. **Lenfant**. The potential use of combining the two techniques could benefit the majority of the 700,000 people having this ailment.

Mr. **Early** And you have the funds to do this trial?

Dr. **Lenfant**. We intend to start it but it may not go as fast as initially planned.

Mr. **Early**. As the Director of this Institute, do you think that is a true savings, Doctor?

Dr. **Lenfant**. We have many, many priorities and we will do our best to handle as many as we can.

INDIRECT COSTS

Mr. **Early**. Let me go back to that, Mr. Williams. The Federal Register says the net 26 percent is an average cost. Now, many institutes, especially the ones in my area, have indirect costs in the range of 35 percent.

But according to this you will now fund no more than 26 percent. Are those institutes going to take a cut this year?

I mean, the effective date in the Federal Register is April 1.

Mr. **Williams** Put a cap on 26 percent. That's right.

Mr. **Early**. So they're going to take that cut. That's a serious cut.

Mr. **Williams**. That depends on the institution. I don't know what the——

Mr. **Early**. Well, let me say this. I think it's over a million dollars for the University of Massachusetts Medical School, I think it's over a million dollars for Harvard, I think it's over a million dollars for B.U., I think it's over a million dollars for Tufts. Do you agree with that, Dr. Wyngaarden?

Dr. **Wyngaarden**. We've heard figures in that range. Yes, sir.

Mr. **Early**. But you're going to elaborate for the record.

Mr. **Williams**. Yes.

RESEARCH CENTERS

Mr. **Early**. Dr. Wyngaarden, you know, we gave you money in 1986 for thrombosis and the high blood pressure centers, even though they weren't in the budget. Are those both started?

Dr. **Lenfant**. Yes, sir.

Mr. EARLY. You also had made a great case for a transfusion medicine center program. Is that underway?

Dr. LENFANT. Yes, sir.

Mr. EARLY. The budget justification indicates that you plan to fund 60 research centers in both 1986 and 1987. However, direct costs for these centers will be reduced by 10 percent in 1986, 16 percent in 1987. Are these averages with centers decreased by varying amounts, or will all the centers be cut by the same amount?

Dr. LENFANT. I cannot answer this question yet, because 24 of our centers are up for renewal next year. And we will have to make decisions, whether——

Mr. EARLY. Will you make the decision?

Dr. LENFANT. Within the amount that is given here of $75.6 million for 1987. Yes, we are able to allocate that to any area within our program.

Mr. EARLY. You're saying "we." I want to get back to that flexibility. I don't think the directors have the flexibility they used to have.

Dr. LENFANT. But my point, Mr. Early, is that it will not be possible to fund next year as much as we are funding this year or last year. Last year we funded centers at $84 million. We will not be able to do that in 1987. Therefore, we will have to make some decisions as to who and what is going to be funded.

Mr. EARLY. How did you arrive at the funding decision? Did you get a figure and were told to back into that?

Dr. LENFANT. I was given an allocation for the centers.

Mr. EARLY. Is that good science? Is that good research? Doctor, I'm so happy with the funding, or if you want to say supplanting, that is coming from the private sector with regard to the Hughes Foundation. I credit that to NIH, because Dr. Frederickson was Dr. Wyngaarden's predecessor.

Are you concerned about that?

Dr. LENFANT. Yes.

Mr. EARLY. Do you have any independence to do anything about it?

Dr. LENFANT. It's very limited.

Mr. EARLY. Doctor, does the Center program play a pretty important role in the prevention and education programs?

Dr. LENFANT. Absolutely. Our Center program has been vital to all of the programs of the Institute. Let me mention something to you that I was looking at last week. And that was how many investigators, people with M.D.'s or Ph.D's, are supported by our Center programs. And I must tell you, I was very surprised to find that 1,276 people with doctorate degrees are working in our Center program. Clearly this number illustrates the importance that this program plays within our overall activities.

Mr. EARLY. Why don't you for the record tell us what specific effects these reductions will have on the Centers?

[The information follows:]

RESEARCH CENTERS

Every program and every center in the research center category of the National Heart, Lung, and Blood Institute (NHLBI) will be affected by the proposed reduction of funding from $84,622,102 in FY 1985 and $82,808,000 in FY 1986 to $75,757,000 in FY 1987, while the number of centers are proposed constant at 60.

The Institute has centers in 11 major clinical program areas—10 programs involving 50 Specialized Centers of Research (SCORs) and a program of 10 Comprehensive Sickle Cell Centers. For five important program areas involving 36 SCORs—hypertension, ischemic (or coronary) heart disease, adult respiratory failure, thrombosis and related clotting problems, and transfusion medicine, and for the 10 Comprehensive Sickle Cell Centers-commitments extend beyond FY 1987. Five other critical SCOR program areas—arteriosclerosis, pediatric pulmonary disease, chronic obstructive pulmonary disease (COPD), pulmonary vascular disease, and occupational and immuno-logical lung diseases—24 of our SCORs in all—will be undergoing competitive renewal in FY 1987. The 36 continuing centers will be substantially reduced by negotiation; on a prorated basis this would be on the order of 15%, but meeting the programmatic needs of the Institute may dictate cuts other than on a prorated basis. There are substantially larger number of highly qualified groups applying than the 24 slots being competed. It is also very likely that the 24 actual awards will have to be made for centers of smaller scope and funding than will be recommended.

More than 1,200 scientists at the doctorate level are currently involved in the research activities of the Institute's 60 centers. It would not be useful to catalog in detail each of the programs and speculate upon the details of impact. However, four of these SCOR program areas—arteriosclerosis, hypertension (with its resultant stroke problems), ischemic heart disease, and chronic obstructive pulmonary disease—are focused on diseases that together account for half the deaths in the United States; thrombosis is an underlying process to a major fraction of these deaths; and the remaining five SCORs and the comprehensive sickle cell centers are all directed at other diseases of major importance.

The centers involve all facets of fundamental biomedical science and each has major clinical programs. Some also have important demonstration and educational activities. Major projects will be delayed, limited in scope, or in some cases indefinitely deferred. Among the scientific activities affected will be molecular biology and controlling factors in the genesis of the arteriosclerosis; neuroendocrine, electrolyte, and emotional influences upon blood pressure; research on reducing scar formation and fatal rhythm disturbances during heart attack, and radioimmunological methods of identifying the site of heart attack; cystic fibrosis, neonatal respiratory distress syndrome and respiratory infections of young children; research on the respiratory failure that commonly accompanies trauma and other causes of acute respiratory failure; research on the respiratory problems associated with a number of occupational diseases and those on an immunological basis; investigations of the fundamental mechanisms involved in the aggregation of platelets and the clotting of blood, as well as in the normal breakup of clots; the development of safer and more effective blood products; and biochemical and genetic studies of sickle cell disease. These are only illustrative of the broad range of basic and clinical research that will be attenuated, delayed or deferred altogether.

Mr. **Early**. Summarize with specifics the effects of the proposed reductions in the Centers program will have on your Institute's program, both immediate and long range, for the record.

Dr. **Lenfant**. We'll do that, sir.

[The information follows:]

Research Centers

The impact of reduced funding for research centers has been summarized as to the resultant decreased and delayed scientific activities. This in turn will delay new and better medical care and preventive medicine.

There is a further facet to the impact of reduced funding for centers. The 10 Specialized Centers of Research (SCOR) programs and the Comprehensive Sickle Cell Centers program have been an effective mechanism for rallying basic scientists and clinicians from a broad range of disciplines to direct their energies in a collaborative fashion upon problems of major importance for the betterment of American health. The implications of reduced funding for such collaborative endeavors will not be lost upon the scientific community. Team efforts will seem to be "out."

Further, the Institute will have less ability to influence research on clinical problems of the highest priority. The centers have been an extremely effective vehicle for such research. The interaction of scientists of diverse backgrounds has provided and tested new ideas rapidly and from multiple perspectives. The centers have provided a means whereby the Institute can catalize such activity and enhance the likelihood that promising areas of research will be successfully exploited. With a decrease in centers—both in funds and as a fraction of the Institute's total research efforts—the Institute's ability to facilitate research by these techniques will be compromised.

MINORITY PROGRAMS

Mr. EARLY. I'll conclude soon, Mr. Chairman.

Your response to Mr. Stokes with regard to minorities, bothers me, as it bothers him, and I'm sure it bothers you. Have you got trials going?

Dr. LENFANT. We do have some studies planned, addressing the issue of prevention and treatment in cardiovascular diseases and pulmonary diseases in minorities.

Mr. EARLY. But the percentage never goes down for them.

We spend money on Central America and Africa. Wouldn't we really lead those countries if we could tell them what they're dying from, and what their birth problems are, and why they're having these problems? You know, we keep going into it, but you never give us a better statistic.

You're the Director of the Institute. When you mentioned to Mr. Stokes that one specific program was postponed, did you fight to keep it going?

Dr. LENFANT. I have argued the needs of the Institute the best I can. Within the Institute we have difficult decisions to make, and I am sure that likewise Dr. Wyngaarden has difficult decisions to make regarding all the Institutes.

Mr. EARLY. I agree with that, and I'm comfortable if you're making the decisions, or if Dr. Wyngaarden is making the decisions.

But I'm absolutely convinced that when Secretary Heckler got sick a year ago, and was out for eight months, OMB took total control. They're running the whole operation, and NIH is going down and down and down.

I really get frustrated, Doctor, when you tell Mr. Stokes, that it isn't getting any better. Spend some money. Make it better.

Dr. LENFANT. Well, sometime, Mr. Early, we may have the opportunity to do some reprogramming within whatever amount we receive.

Mr. EARLY. But you told me you don't have the flexibility to reprogram.

Dr. LENFANT. Well, as yet this year we haven't made any requests. But I think with the apportionment as it is today, among approximately 15 different categories in our budget, our ability to do reprogramming and rebudgeting is going to be limited.

Mr. EARLY. Dr. Lenfant, this Committee, and the House and the Senate, gave a specific number of grants and money to Dr. Wyngaarden to give him more autonomy. But I think what's happening is it's giving OMB the vehicle to eliminate that autonomy.

I don't think Mr. Miller should make these decisions.

I really respect NIH so much, but I'm really perturbed that the directors are not speaking up publicly. You're a good soldier, but those problems are everywhere. We're not getting anything done. We're not moving.

We used to always give you a little more. Now, you're even asking for a little less.

I've used my time. Mr. Chairman, may I ask one further question on AIDS?

Mr. STOKES [presiding]. Sure.

AIDS

Mr. EARLY. What bothers me——

Mr. HOYER. If the gentleman would yield, I don't intend to ask any further questions, because I'm convinced that the questions you're asking are pointed, and the ones I want to ask. And I'll yield my time to you.

Mr. EARLY. Thank you.

On AIDS, nothing bothers me more than when I see a 12 year old hemophiliac with AIDS. Now if someone gets AIDS through their promiscuity, that's their business. I'm sorry for them, too. But not like I am for a 12 year old hemophiliac that contracts it through a blood transfusion.

Now, you say that you've got a new heat process that you think improves the blood?

Dr. LENFANT. Yes.

Mr. EARLY. Can you guarantee to this Committee that the blood is good?

Dr. LENFANT. I would say that today it is as good as it can be. Considering that in this country each year we are using approximately 18 million units of blood or blood products, I cannot guarantee to you that each of these 18 million units are not contaminated, but I can guarantee most of them are not.

Mr. EARLY. You say you're doing more studies. Are you satisfied that you're doing enough?

Dr. LENFANT. There are many other things that should, and probably will be done.

Mr. EARLY. With this budget, with the 1987 budget?

Dr. LENFANT. Well, it depends on the flexibility that we will have, and as you know, for next year the AIDS money has been placed in the Assistant Secretary's office. Dr. Wyngaarden is confident that this money will come back to NIH. And I am confident that Dr. Wyngaarden will give us our share.

Mr. EARLY. What was your budget that you submitted to Dr. Wyngaarden?

Dr. LENFANT. It was $1,029,000,000.

Mr. EARLY. They only cut you 25 percent. Dr. Wyngaarden, what did you submit to OMB for this Institute?

Dr. WYNGAARDEN. The Department submitted $937,597,000.

Mr. EARLY. So, therefore, here comes Mr. Miller. He's going to tell us who is sick and who is not sick.

I really wish the directors were like they were in the 1970's, Dr. Lenfant, and I respect you. But I really think you've got to charge this issue.

You're not being treated the same as all the other programs are now, because of that indirect cost issue which I addressed. Defense hasn't taken it. We can say that in most arguments, but none of the other agencies have either.

Thank you, Mr. Chairman.

Mr. **Hoyer**. Mr. Chairman, I said I wasn't going to ask any questions, but I would like to make an observation here that I think is accurate.

This Committee is not going to allow NIH to be cut as has been proposed by the administration. I think Mr. Miller knows that full well. It's not a question of you, Doctor. I think in order to get to the $144 billion deficit, he cut in some areas that he knew weren't going to be cut, and weren't going to be cut, and has made our job, therefore, because the budget submitted to us is not a realistic assessment of the priorities of this nation, even more difficult in the Congress of the United States.

And I think that's why we find—and Mr. Early and I had had the discussion as a result of my discussion with Dr. Wyngaarden yesterday with respect to the fact that there was almost—well, on paper a billion dollars—but because of the AIDS transfer to the Secretary's office, about $805 million, $807 million cut between the Department and OMB. I am convinced that that was just picking up a billion dollars to get down to an arbitrary Gramm-Rudman figure, that they don't expect to happen, and in my opinion honestly don't feel would be a responsible action in terms of public policy.

Thank you, Mr. Chairman.

Mr. **Early**. Mr. Chairman, may I make one more point?

Mr. **Stokes**. Sure, Mr. Early.

Mr. **Early**. How long have you been director?

Dr. **Lenfant**. Not quite four years.

Mr. **Early**. It's a tough four. We usually go down hill. We're going up hill now.

I asked Dr. DeVita today and he responded that he didn't think he had the autonomy he use to. Has your autonomy and independence as Director of this prestigious Institute diminished?

Dr. **Lenfant**. Yes.

Mr. **Early**. Would you elaborate on that for the record a little, without getting yourself in too much trouble? [Laughter.]

[Laughter.]

[The information follows:]

Autonomy of the Director

Our appropriation is divided into several cost categories. Within these cost categories, the Institute director and Institute staff can decide which approved grants are funded, which research contract programs are funded and so forth. Some of these cost categories such as heart and vascular diseases, lung diseases, and blood diseases and resources, intramural research, and research management and support, have been used as parameters and have controlled our actions for several years. Recently, however, several new categories have been added through a revised apportionment process. These new categories limited my flexibility as Institute director, and place new limits on the changes I can make as Institute director.

For example, competing and noncompeting research centers are now controlled as two separate items through the apportionment process. The Institute Director cannot make any change from the budgeted amount in these two categories. If any change is needed, whether the change is to take advantage of scientific opportunities or whether it is to facilitate the management of a program, the approval of the Director, NIH, is required. Depending on the nature and the amount of the change, approval of the Assistant Secretary for Health, DHHS; the Assistant Secretary for Management and Budget, DHHS; the Office of Management and Budget; and the Chairmen of both the House and Senate Appropriations Committees may also be required.

There are several areas where additional flexibility would be necessary to achieve better management of scientific opportunities. For example, each year some of our 11 distinct centers programs may recompete for additional funding. At the time the budget is put together, it is not known whether some of the applications will propose high quality research that may cost somewhat more than the amount for competing research centers in the budget. Prudent management may dictate that the Institute Director move a small amount of funds to competing research centers from noncompeting research centers, because, for example, unanticipated savings in ongoing centers have become available.

Dr. **Lenfant**. I really like my job. I would like to keep it.

Mr. **Early**. That's the point, Dr. Lenfant. Even if we give you the reduced amounts, you've got to make a big contribution. If there's any place the United States can lead the world, as they've led in the past, it is with you people.

MINORITY TRAINING

Mr. **Stokes**. Dr. Lenfant, I have a couple of additional questions I want to ask you.

Tell us what your Institute is doing to increase the number of minorities supported through institutional training grants that go to non-minority institutions?

Dr. **Lenfant**. We work very actively, and I would say effectively with the training program directors to encourage them to reach out in all the strata of emerging scientists to provide further training. And over the years we have seen a substantial increase in the number of minority trainees.

In addition, our Institute is supporting a number of special training programs which are given to non-minority institutions for the training of minority students.

All together, we have approximately 20 or 22 such programs.

Mr. **Stokes**. In 1984, your Institute awarded $5.4 million to minority institutions, with $3.7 million going to historically Black colleges.

What are your comparable figures for fiscal year 1985, and tell us what your goals are for 1986 and 1987?

Dr. **Lenfant**. I will provide the specific answer for the record.

[The information follows:]

Minority School Programs

In FY 1985, the NHLBI awarded $4.9 million to minority institutions. Of this amount, $4.3 million was awarded to historically black colleges. In FY 1986 it is estimated that $5.1 million will be awarded to minority institutions, including $4.5 million to historically black colleges. The FY 1987 estimate is $4.8 million to minority institutions, including $4.2 million to historically black colleges.

Dr. **Lenfant**. I would like to say, however, Mr. Stokes, as we describe in the Institute "Report on Research Related to Minorities", in 1983 the Institute supported approximately $24 million for research related to minority health issues, some of that to minority institutions.

Last year that amount was $48 million, and again part of it was to minority institutions. We will have the specific breakdown for the record.

Mr. **Stokes**. Doctor, do you establish goals for your senior administrators for addressing these minority program and personnel matters?

Dr. **Lenfant**. Not goals, Mr. Stokes, but four or five times a year we have discussions among the senior executive staff of the Institutes to address health issues related to minorities. With regard to the staffing of the Institute with minorities and women, our Institute has a good record, and we really reach out to all possible opportunities to enhance the minority staff of our Institute, to increase the research capability of minority institutions, and to initiate programs which are addressing minority health issues.

Mr. **Stokes**. But, in the absence of establishing some goals, how do you measure progress in those areas? If you just sit around and talk about it, that's one thing. It's something else if you say by a year from now we ought to have accomplished this or accomplished that. There should be some measurable standard by which you can evaluate progress.

Dr. **Lenfant**. Well, we can demonstrate the effectiveness of our talking around, by showing that in 1983 the NHLBI committed $26 million to minority research, and two years later the amount was $48,706,000. And even though we don't have a goal, the numbers demonstrate the effectiveness of our plans.

We can also say that with regard to programs that are specific to minority institutions.

Now, I should also say that all the employees of the Institute who are in the Executive Service, have a requirement in their performance appraisal, as I have in mine, to demonstrate that they are meeting affirmative action objectives.

Mr. **Stokes**. Doctor, please supply for me for the record this information for SES positions: your senior level administrative level positions; your senior level professional positions in your Institute; the current number of all such positions in your Institute; and, the current number of these positions that are occupied by Blacks and or other minorities.

[The information follows:]

POSITIONS OCCUPIED BY BLACKS OR OTHER MINORITIES—NHLBI SENIOR INSTITUTE STAFF

	GS 13–15[1]	GM 13–15[2]	CO[3]	SES[4]	Total
Minority females:					
Number	5	2	1	1	9
Percent of total	7	2	2	6	4
Nonminority females:					
Number	23	26	6	2	57
Percent of total	30	29	10	12	23
Minority males:					
Number	8	8	1		17
Percent of total	10	9	2		7
Nonminority males:					
Number	40	54	52	14	160
Percent of total	53	60	86	82	66
Total number	76	90	60	17	243
Total percent	100	100	100	100	100

[1] GS refers to General Schedule personnel.

[2] GM refers to Performance Management and Recognition System personnel.

[3] CO refers to PHS Commission Corps personnel.

[4] SES refers to Senior Executive Service personnel.

TRANSFUSION TRANSMITTED DISEASES

Mr. **Stokes**. Is AIDS the only disease that can be transmitted by blood transfusions?

Dr. **Lenfant**. No. Hepatitis B, although that one is pretty much under control, the so-called non-A, non-B, hepatitis, and another form of hepatitis which has been described not too long ago called the delta hepatitis, and cytomegalo virus infections can be transmitted by blood transfusion.

Mr. **Stokes**. Are you satisfied that we have enough resources in order to keep the nation's blood supply safe, and that we're doing all that we can do in this regard?

Dr. **Lenfant**. We do the best we can and we are pretty effective. As I mentioned a few minutes ago, the risk of contamination, or the transmission of AIDS by way of blood transfusion probably has not been completely eliminated, but it has been greatly reduced.

On the other hand, there is the magnitude and the importance of the blood supply in this country. As I said, 18 million blood or blood product units are transfused each year to approximately 3.5 million people. The risk of disrupting the blood supply is great. It can occur at any time, and if we have any doubt about that, all we have to do is remember the history of AIDS in this country. Therefore the answer to your question is we could probably do much more, and we should do much more. But here again, we will have to sort out our various priorities.

I should say that within the President's budget, we have a couple of initiatives that will address the delta hepatitis that I mentioned earlier.

Mr. **Stokes**. Mr. Early, anything further?

Mr. **Early**. I have some further questions which I will submit for the record.

Mr. **Stokes**. I may have some additional questions which I will submit for the record also.

Dr. Lenfant, it's always a pleasure to have you here before us here, and we appreciate your presentation, and your participation in answering our questions here.

Thank you very much.

The meeting is adjourned till 10:00 o'clock tomorrow morning.

[The following questions were submitted to be answered for the record:]

CHOLESTEROL

Mr. Conte. I still think that it's much harder for people to get a handle on their cholesterol levels than it is on their blood pressure, because you have to go to a doctor and ask for a cholesterol test. Has there been any progress in making cholesterol testing more accessible and available?

Dr. Lenfant. There are now several new instruments that measure cholesterol in a matter of minutes, and use fingerstick blood specimens rather than venous blood. These instruments are portable and have the potential for screening large groups of people easily and inexpensively. Pilot tests of this new equipment in community screenings have been met with considerable public interest. The NHLBI is currently funding research to develop model systems for blood cholesterol screening using these devices.

However, a significant problem with blood cholesterol measurements is that different methods of testing yield different results and, without scrupulous care, repeated tests with the same technique will not give as consistent results as necessary. Thus we are supporting activities to achieve consistency within and between methods.

CENTERS

Mr. Conte. Any problems with regard to the Centers line in the FY 1987 budget request?

Dr. Lenfant. The FY 1987 request is $75,757,000 for centers; this is $7,057,000 less than the 1986 revised level for 60 centers, and $14,626,000 less than the estimated full cost requirement for 60 centers. Five of our Specialized Centers of Research (SCOR) programs--on arteriosclerosis, on pediatric pulmonary diseases, on chronic obstructive pulmonary disease (COPD), on pulmonary vascular disease, and on occupational and immunological diseases, 24 of our SCORs in all--will be undergoing competitive renewal in FY 1987. Through negotiation we will have to reduce funding from recommended levels for both competing and noncompeting SCORs and we will have to eliminate favorably recommended projects entirely in some competing SCORs.

LUNG DISORDERS

Mr. Conte. In contrast to the trend in deaths due to heart disease you indicate that the trend in chronic obstructive pulmonary disease has been upward. By the way, is chronic obstructive pulmonary disease the same as emphysema?

Dr. Lenfant. Chronic obstructive pulmonary disease, or COPD, involves chronic and irreversible airflow obstruction and it includes both emphysema and chronic bronchitis. In 1984, there were 66,000 deaths in the United States from chronic obstructive pulmonary disease, the fifth leading cause of death. Between 1974 and 1984, the death rate rose by 39 percent, making this the fastest rising major cause of death in the United States. Because COPD is a chronic condition, economic costs for care of patients who suffer from this disease are enormous, estimated to be $28 billion in 1983.

Mr. Conte. Is smoking the main reason for this trend?

Dr. Lenfant. Yes. The 1984 Surgeon General's Report on Smoking and Health was devoted to an examination of the evidence related to smoking and COPD. The conclusion from the report was: "Cigarette smoking is the major cause of chronic obstructive pulmonary disease in the United States for both men and women. The contribution of cigarette smoking to chronic obstructive pulmonary disease morbidity and mortality far outweighs all other factors."

Some of the other risk factors examined included air pollution, familial factors, occupation, childhood respiratory illness, airways hyperreactivity, passive exposure to tobacco smoke, respiratory illnesses, and socioeconomic status. The only widely prevalent predictor for developing or dying of COPD is smoking behavior. Simply put, in the absence of cigarette smoking, clinically significant COPD is very rare.

CYSTIC FIBROSIS

Mr. Conte. I was interested in the statement in your justification suggesting that parents of children with cystic fibrosis (CF), and therefore likely to have a CF gene present, seem to be more susceptible to the effects of smoking and aging on pulmonary function than the average. Does this suggest there is a health effect of carrying a cystic fibrosis gene even when it is not expressed?

Dr. Lenfant. Yes. The parents of children with cystic fibrosis are more likely to have airways that are hyper-reactive to certain chemical and physical challenges. From research with smoking and chronic obstructive pulmonary diseases (COPD), we know that those who have hyperactive airways are more likely to develop COPD. Thus parents of children with CF would seem to have a higher risk for developing the pulmonary complications of smoking. And interestingly, these relationships are scientifically provocative because they raise some possibilities about genetic bases for the observation that smoking may be even more harmful for some people than others.

AIDS

Mr. Conte. Now that we have a screening process for antibodies to AIDS, is the nation's blood supply safe from spreading AIDS?

Dr. Lenfant. The nation's blood supply is much safer since implementation of general screening for antibody to the AIDS virus (HTLV-III), but we can't be absolutely certain about its safety. In August, 1985, the American National Red Cross reported that of 1,027,786 units of blood tested for antibody to HTLV-III, 1,723 were found to be repeatedly reactive with the screening test; 333 of these reactive units were confirmed to have HTLV-III antibodies by a different type of test. Units that react on the screening test are not transfused and are discarded. Since implementation of general screening, the blood banking community has tested millions of units of blood, and thousands of potentially infectious units have been discarded. This practice has contributed significantly to the improved safety of the nation's blood supply.

Although the current testing probably identifies almost all blood infected with HTLV-III, there may be individuals who are in the early stage of infection and have not yet developed antibodies to the virus. Therefore the NHLBI has recently released a request for proposals to support development of more specific tests for the AIDS virus including detection of the virus or its components. Such tests should make the nation's blood supply even safer than it is today.

Mr. Conte. Have there been any cases documented of AIDS being spread through transfusions after the blood screening process was put in place?

Dr. Lenfant. Since implementation of blood screening for antibody to the AIDS virus (HTLV-III), there have been no documented cases of AIDS as a result of transfusion of screened blood. Because AIDS may not develop until several years after infection, cases of transfusion-associated AIDS will continue to appear among individuals who received transfusions before screening was available.

Mr. Conte. Why, in your justification, do you say that the current ELISA tests for screening blood donors are not entirely satisfactory?

Dr. Lenfant. The ELISA tests give substantial false positive results and also very rare false negative results.

Commercial assays to detect antibody to the AIDS virus contain partially purified, disrupted virus as a source of viral antigen. The purified, disrupted virus usually contains contaminants from the cell line in which the virus was grown; these contaminants can cause non-specific, or false positive, reactions. Consequently, if a sample is found to be repeatedly reactive using the initial screening test, a second test must be performed as a confirmatory procedure. There is, therefore, a need for antigen preparations that are more pure and better defined than existing preparations. Investigators supported under a special NHLBI program have successfully synthesized a segment of the outer coat of HTLV-III in the laboratory. Tests incorporating such a synthetic component should be more specific than currently available tests since they are devoid of cellular protein that might elicit false-positive reactions. Such improved assays might reduce or eliminate the need for expensive confirmatory tests.

The current test procedures probably identify almost all the units of blood that are infected with HTLV-III. However, there may be some individuals who are at an early stage of infection, or who have an impaired immunologic response, who have not developed antibodies and would thus be negative in the screening test. The NHLBI is concerned about being able to detect such infectious units and has recently released a request for proposals (RFP) that would support development of tests for virus and viral components in blood and blood components.

Mr. Conte. Your justification also says the Institute is supporting the development of an immune globulin which may prove useful in certain populations in preventing AIDS after exposure to the virus. Can you describe?

Dr. Lenfant. The NHLBI supports a contract to develop an immune globulin preparation that may prove useful in preventing AIDS after exposure to the AIDS virus. Investigators are testing the sera of homosexual males for antibodies to HTLV-III that will actually neutralize the virus. Once adequate concentrations of virus neutralizing activity are demonstrated in the blood of these volunteers, large quantities of plasma will be collected, pooled, and an investigational product suitable for clinical trials will be developed under the contract. The immune globulin preparation will be tested in appropriate animal models for safety and efficacy; these studies also would identify the appropriate stage of viral infection for effective treatment. Once the safety and efficacy of the preparation are established in animal models, clinical studies in human populations will be developed.

AIDS

Mr. Conte. Do you have sufficient funds in the FY 1986 budget, assuming no rescission, and in the FY 1987 budget request to do all the AIDS work that you think would be productive?

Dr. Lenfant. The $11.2 million budget for NHLBI for AIDS in fiscal year 1986 will be adequate for this year's needs. The $17.1 million in the President's budget for FY 1987 is sufficient to permit the NHLBI to support foreseeable productive activities.

COOLEY'S ANEMIA

Mr. Conte. For a number of years now, I remember discussions about the possibilities for both Cooley's anemia and sickle cell, of reactivating the production of a type of hemoglobin normally produced in the fetal stage. Has there been any progress in actually stimulating the production of this kind of hemoglobin in these patients?

Dr. Lenfant. The initial results of reactivating fetal hemoglobin production using 5-azacytidine in patients with Cooley's anemia and sickle cell disease were encouraging and led to the search for other agents that might act in a similar fashion, but with less potential risk to the patient. Such an agent, hydroxyurea, has been used in a small number of severely affected sickle cell disease patients producing a significant increase in fetal hemoglobin and slight improvement in clinical symptoms. Results with Cooley's anemia patients were not as promising. Further studies are proposed to determine the optimum dose and schedule of hydroxyurea to achieve maximum biologic effect with minimal risk to patients with sickle cell disease.

RESCISSION

Mr. Conte. Why is it that the rescission proposed for NHLBI is larger than any other Institute?

Dr. Lenfant. While the total amount of the FY 1986 rescission for research project grants was mandated by OMB, the Office of the Director, NIH, had the responsibility of allocating the total reduction and assigning specific rescission amounts to each Institute. The amount of each Institute's rescission was determined in two steps--a simple proration of the total rescission was first computed against each Institute's funding for research project grants and then these amounts were adjusted further to reflect NIH research priorities.

BUDGET FLEXIBILITY

Mr. Conte. As the budget tightens and stretches and strains, do you feel you have sufficient control and flexibility over the Institute's budget to manage things adequately?

Dr. Lenfant. Our appropriation is divided into several cost categories. Within these cost categories, the Institute director and Institute staff can decide which approved grants are funded, which research contract programs are funded and so forth. Some of these cost categories--such as heart and vascular diseases, lung diseases, blood diseases and resources, intramural research, and research management and support--have been used as parameters and have controlled our actions for several years. Recently, however, several new categories have been added through a revised apportionment process. These new categories limit my flexibility as Institute director, and place new limits on the changes I can make as Institute director. This new process requires that any changes in our operating plan be cleared with the Office of the Director, NIH, and the Office of Management and Budget.

Mr. Conte. If not, where are the problems?

Dr. Lenfant. The problems occur because the fiscal status of the Institute is constantly changing for many very good reasons. Some of these factors are programmatic; others relate to good management and common sense. Among the factors causing change are the development of new research opportunities and the different pace at which various areas of science develop. Other managerial factors are indirect cost adjustments, the difficulty in estimating the cost of a given group of research grants, and the relative balance among scientific topics and the balance among mechanisms of research support.

Recent Congressional actions, such as specifying a minimum number of new and competing research grants, has meant that the Institute directors can no longer make some important changes that they previously could make. If any change is needed, whether the change is to take advantage of scientific opportunities or whether it is to facilitate the management of a program, the approval of the Director, NIH, is required. Depending on the nature and the amount of the change, approval of the Assistant Secretary for Health, DHHS; the Assistant Secretary for Management and Budget, DHHS; the Office of Management and Budget; and the Chairmen of both the House and Senate Appropriations Committees may also be required.

CONSTRUCTION GRANTS

Mr. Conte. What awards were made with the $3.3 million in construction funds in FY 1985, what are your plans for FY 1986, and why was no construction money proposed for FY 1987?

Dr. Lenfant. In FY 1985, the Institute awarded eight shared research facility renovation and construction grants with the $3.3 million. At this time, the Institute plans to support four to five grants in FY 1986. Because of many competing needs for the amount of funds available in the FY 1987 President's Budget, no funds were requested for these grants.

AVERAGE GRANT COSTS

Mr. Conte. Can you give me an idea of what average increase in grant awards over last year is anticipated in this budget? Can you also give me the average rate of increase over the past 5 years, and your explanation for this rise.

Dr. Lenfant. The Institute anticipates that the increase in average cost for research project grants from FY 1986 to the FY 1987 President's Budget will be approximately 2.8 percent for noncompeting and 5.5 percent for competing before indirect cost savings are applied. If the administrative cost portion of indirect costs is capped at 20 percent, the increase in average cost will be 0.4 percent for noncompeting and 3.1 percent for competing.

The average rate of increase for research project grants in the past 5 years has been 11.7 percent per year, from $114,800 in FY 1980 to $181,800 in FY 1985. There are several factors responsible for the fact that this rate is greater than the general escalation of things all around us. Research is progressively more complex and sophisticated and therefore more expensive; the advanced technology is more expensive and the magnitude of the effort for many current questions must be greater. Also, in recent years we have been awarding a progressively smaller fraction of approved applications--only the best of the best--and for a long time we have found that on the average, the better the research the more expensive it is.

RESEARCH TRAINING

Mr. Conte. Do you view the decrease proposed in the training budget as significant?

Dr. Lenfant. The revised FY 1986 budget allocated to the NHLBI a total of $38.4 million to support 1,627 full time training positions. The FY 1987 training budget will be reduced by a total of $4.7 million. This sum will allow the Institute to support 127 fewer full time training positions than it is supporting in FY 1986. The Institute believes, that the 1500 full time training positions provided in the FY 1987 budget will support the training of many of the best young people who would like to undertake a research career in heart, lung, and blood disease.

DOWNWARD NEGOTIATIONS OF DIRECT COSTS OF GRANTS

Mr. Roybal. Can you anticipate, in a general way, how the 1986 and 1987 downward negotiation of grants might affect the investigator's ability to draw scientific conclusions from a reduced level of activities or his need to seek followup funds at the conclusion of the original grant period in order to achieve the original research objectives?

Dr. Lenfant. For this Institute, the downward negotiation of funds to be awarded to research grants will be much greater in 1987 than is currently the case. Most reductions are made in categories outside personnel, such as supplies, equipment, and various services. The funding levels anticipated for 1987 will cause constraints on research activities and will necessitate reductions in personnel; savings realized in any category are not likely to allow optimum laboratory operation plus retention of personnel. Thus, experienced people may be lost and the avenues of research may be even more limited than in the current year. Projects will require a longer time to complete. Many scientists may pursue only studies with the highest likelihood of solid results, further jeopardizing the creativity of this community.

Mr. Roybal. What are the investigators telling you about what categories of expenditures would most likely be affected?

Dr. Lenfant. Categories of expenditures most affected are first, those deferrable costs such as supplies, new equipment, hiring of technicians, and use of outside consultants. This initially reduces costs allowing experiments in progress to be maintained as long as possible. For the long term they are planning reductions in the number of experiments, in the number of animals used in experimental studies, number of patients in clinical studies, and postponement of followup on experiments that would confirm or provide more definitive research findings.

Current negotiated reductions are primarily in equipment, supplies, and other services. In 1987, in order to achieve the Institute's budgetary goals and to fund new research grants, additional reductions will be necessary. These reductions will include personnel in addition to the other categories. Investigators in small laboratories indicate that this action will create problems for them as they have very few personnel working on grant supported research. The situation will also create problems for better established laboratories with very experienced personnel for whom other sources of support must be found or their services will be lost.

NATIONAL EDUCATION PROGRAMS

Mr. Roybal. What is the current plan, in terms of funding and activities, for the National Cholesterol Education Program and how would the 1987 budget request affect the program?

Dr. Lenfant. We do not have a specific budget category for the National Cholesterol Education Program. Funds for this effort can be found in a support services contract, a mass media contract, in pertinent workshops, some survey and data acquisition activities, and in our publications budget. The support services contract, for example, gives us the resource to operate a Coordinating Committee comprised of more than 20 national organizations such as the American Medical Association, the American Public Health Association, and the American Heart Associaton. There are three meetings a year for the full Committee. There are studies under way to develop progam guidelines and treatment recommendations that will eventually be endorsed and promulgated by the overall Committee. The support contractor will be spending $900,000 of our funds in FY 1987. The mass media contract will require $300,000 to produce the planned television and radio spots and to print ads to carry cholesterol education messages to the public.

The 1987 budget will curtail or postpone some activities that were planned to provide the new program with needed data or to help it get updated information to the health professions and to the public. For example, we wanted to conduct a survey among nurses and dietitians to see what their knowledge level is regarding the benefits of lowering elevated cholesterol, as well as their professional and personal practices. This would serve two purposes. One, it would provide us with baseline data against which we could measure the impact of some of our professional education activities. And, two, it would suggest to us what our educational priorities should be in trying to more effectively activate the nurse and the dietitian in this area. We originally scheduled this survey to be implemented in FY 1986. However, because of budget considerations we postponed it until FY 1987. Given the many competing demands for existing dollars, however, I am not sure we will fund it in 1987.

Another area of concern is that of publications. We rely on publications to carry our messages to a wide array of audiences. In FY 1986, however, we cut back considerably on our publications budget, and we are likely to do the same in 1987. For example, since we are advocating that citizens ask their doctor to check their cholesterol level during their next scheduled visit, we felt it would be useful for doctors to have a patient education booklet that might be titled--"So, You Have Been Told You Have High Blood Cholesterol. What Do You Do Now?" Again, because of budget considerations, this and many other publications were not produced in FY 1986 and may not be produced in FY 1987.

Travel is another category that we reduced in FY 1986 and will likely have to do so again in FY 1987. This is particularly important for the new cholesterol effort because organizations around the country want NHLBI staff to come and explain the new program to them so they can plan on how best to support the national effort. We continue to turn down requests because of limited travel funds. Also, we have expanded the scope of the Ad Hoc Committee on Minority Populations to include the matter of blood cholesterol in minority groups.

I should point out that, even with the reduced budget, we expect to go forward with the implementation of the National Cholesterol Education Program and we will expect to have some beneficial impact on the health of the American public. This is an important area, and it has a priority within the Institute.

Mr. Roybal. What is the current plan, in terms of funding and activities, for the National High Blood Pressure Education Program and how would the 1987 budget request affect the program?

Dr. Lenfant. Again, the National High Blood Pressure Education Program is not a line-item in the budget. It, too, receives its resources through a number of activities and mechanisms, including a support services contract, a media contract, workshops, and survey activities. Approximately $1,200,000 of our funds will be spent by the contractor in FY 1987 for this support service, which will include the administration of Coordinating Committee activities similar to that described for cholesterol. The area where we see reduced activity that may adversely affect the program is in publications and travel. We had to significantly reduce the number of publications we could produce in FY 1986 and will probably have to do the same in FY 1987.

I would like to add a point about the investment of the NHLBI resources in these two national education programs. We are convinced that the key to the success of the high blood pressure effort for the past 14 years has been the fact that its activities are built on a solid scientific foundation giving it a credibility which is essential to our role of coordinator and catalyst. The same, we feel, will be borne out in the case of cholesterol. The reason we can have these education programs to improve the Nation's health is that we have made past investments in the research upon which the programs are built.

IMPACT OF BUDGET REDUCTIONS

Mr. Roybal. The 1987 budget shows substantial reductions from the 1985 level in contracts and other services. How much, if any, of the scientific work that was being done under the contract mechanism is being terminated prematurely or being modified in ways that will impact significantly on the scope of activities or the time frame for completing the work?

Dr. Lenfant. Currently, no research supported by contract is being terminated prematurely, but many studies are being modified to limit their scope, increase their duration, or delay their implementation -- and thus postpone their completion. For example, the Institute may have to delay its Post Coronary Artery Bypass Graft Study to FY 1987 and perhaps FY 1988. The Institute has also delayed the biventricular assist and replacement devices program. Other programs that have been affected are the thermal energy program; the device readiness program; the thrombolysis in myocardial infarction clinical trial; the studies of left ventricular dysfunction program; the cardiac arrhythmias treatment study; a study of obesity and cardiovascular disease in women; the diagnosis of pulmonary embolism trial; the prevention of chronic obstruction pulmonary disease study; the high frequency ventilation clinical trial; and the clinical course of sickle cell disease study.

Mr. Roybal. Would any area of extramural or intramural research be affected disproportionately by these reductions, and if so, were those areas chosen for reasons of program priority or because of categorical expenditure targets imposed upon NHLBI?

Dr. Lenfant. In the extramural program, in an effort to maintain research project grants at as high a level as possible, other mechanisms have had to be reduced in recent years to levels I believe may not result in the best balance. Specifically, while the research project grant line of the budget has grown from 54.3 percent of the extramural budget in FY 1978 to 71.9 percent in FY 1987, research contracts, with which we support most of our clinical trials, has declined from 23.1 to 7.5 percent and research centers has declined from 13.8 to 10.9 percent.

It should also be noted that constraints upon the intramural research program as a whole have resulted in measurable decreases in the intramural research effort. That program has decreased from 8.0 percent of the total Institute budget in FY 1978 to 7.1 percent in 1987, a period during which the total extramural program went from 85.9 percent to 88.3 percent.

IMPACT OF BUDGET REDUCTIONS

Mr. Roybal. What impact would the 1987 reduction of 25-percent from the 1985 level in supplies and equipment have on the intramural program and clinical center activities?

Dr. Lenfant. The 10 laboratories and 7 clinical branches of the intramural division could not absorb a 25-percent reduction in supplies and equipment and simultaneously maintain the current number or level of research activities. Provisional plans include major reduction or elimination of three laboratories engaged in chemical and pharmacological research because their loss would have less impact on the remaining activities than would the loss of any other laboratories or clinical branches. In addition, selective reductions would be made in other programs, including research on experimental atherosclerosis and clinical hypertension. These actions would accomplish part of the reduction.

To accomplish a 25 percent reduction in supplies and equipment while maintaining a viable, balanced intramural division, selective reductions of the activities of the 5 major clinical branches would be unavoidable. Research activities likely to be affected include: continual, 24-hour electrocardiograms using Holter monitors to evaluate cardiac function of patients; the study in patients and normal volunteers of the relationship between abnormal plasma lipoproteins and disease of the heart and vascular system; studies in monkey and, later, clinical trials of gene replacement therapy for the possible alleviation of certain genetic diseases; development of novel therapeutic approaches to the treatment of pulmonary emphysema, including that aggravated by smoking; studies of coronary artery abnormalities of animals on experimental diets; development and clinical testing of prosthetic heart valves; and clinical evaluation of the results of bypass surgery.

NHLBI INITIATED MINORITY PROGRAMS

Mr. Stokes. Dr. Lenfant, in FY 1985, awards were made by your Institute under the Minority School Faculty Development Awards Program. Why were no awards made under the Minority Institutional Research Training Program, the Visiting Professor Program for Minority Institutions and the Research Fellow Program for Investigators at Minority Institutions?

Dr. Lenfant. In FY 1985, the National Heart, Lung, and Blood Institute continued its commitment to programs directed toward stimulating minority involvement in biomedical research. Five new awards were made in the Minority School Faculty Awards Program. While the Institute retained its interest in both the Minority Institutional Research Training Program and the NHLBI Visiting Professor Program, no new awards were funded in either program because of a limited response from the community. We received no new applications for the NHLBI Visiting Professor Program and the one application submitted for the Minority Institutional Research Training Program was deferred at the request of the applicant.

The Institute did receive four applications for the NHLBI Research Fellows Program for Investigators at Minority Institutions, a program designed to bring investigators into our intramural laboratories. However, all participants in the program are counted against the NHLBI allocation of full time equivalents (FTEs). With the reduction in FTEs available to the Institute we decided not to make any awards.

Mr. Stokes. What are the planned allocations for these initiatives in 1986 and 1987?

Dr. Lenfant. For the Minority School Development Program we anticipate making nine awards ($506,000) in FY 1986 and six awards ($285,000) in FY 1987.

For the Minority Institutional Training Program we anticipate making at least one award ($105,000) and perhaps two or three in FY 1986 depending upon the quality of applications. FY 1987 awards will be dependent upon available funds and quality applications.

No specific allocations have been made for the Visiting Professor and the Research Fellows Program. Future allocations will depend upon interest expressed in the programs, and the funds available to the Institute.

MINORITY PROGRAMS

Mr. Stokes. Please provide a list of the institutions receiving awards and the amounts received.

Dr. Lenfant. Faculty members from the following Institutions received Minority School Faculty Development Awards (K-14).

Charles R. Drew Postgraduate Medical School	$75,081
Meharry Medical College	$62,000
Rust College	$54,000
Texas Southern University	$52,000
Winston Salem State University	$40,000

Mr. Stokes. How much was allocated for the minority summer program for pulmonary research in 1985 and what is planned for 1986 and 1987?

Dr. Lenfant. In FY 1985, one award ($34,000) was made under the Minority Summer Program for Pulmonary Research. In FY 1986 and FY 1987 allocations are dependent upon quality of applications.

CLINICAL TRIALS

Mr. Early. Will you be able to start any new clinical trials in FY 87?

Dr. Lenfant. At the FY 1987 request level we do not plan to fund any new clinical trials.

Mr. Early. If not, why not?

Dr. Lenfant. The decision to fund major long term clinical trials requires a commitment on the part of the Institute to carry out an approved protocol that will provide statistically valid answers to the research questions that are asked. Frequently, these trials are relatively inexpensive to begin, but require larger amounts of funds as patients are recruited into the study. The Institute is already committed to several large trials for which the funding schedule has been modified. Based on the total funds currently available to the Institute and the funds available for research and development contracts, the mechanism we feel is most effective for clinical trials, the Institute cannot make a long range commitment to new trials in 1987.

Mr. Early. Doctor, will you have to curtail any ongoing clinical trials with your FY 87 budget request and, if so, which ones?

Dr. Lenfant. We have had to narrow the scope, prolong the duration or delay the initiation of a number of clinical trials--trials that involve the management of acute myocardial infarction with thrombolytic drug and balloon recanulization of occluded coronary arteries (Thrombolysis in Myocardial Infarction), chronic heart failure with new drugs (Study of Left Ventricular Dysfunction), bypass graft patency after coronary surgery, angina pectoris by percutaneous transluminal coronary angioplasty (PTCA) or bypass surgery, the neonatal respiratory distress syndrome with high frequency ventilation, and pulmonary embolism with a thrombolytic drug--and a trial of therepeutic strategies to prevent chronic obstructive pulmonary disease and a trial of antiarrhythmic drugs to prevent sudden death in survivors of heart attack who have rhythm disorders.

Mr. Early. Are there any high priority clinical trials which are ready but cannot be initiated because lack of funds in the FY 1987 request. If so, please provide a list of these, along with a brief description and the associated costs, including first year costs.

Dr. Lenfant. Yes, there are several new clinical trials that the NHLBI feels merit support but cannot be funded under the FY 1987 budget request. A list follows:

1. Bypass Angioplasty Revascularization Investigation

   This clinical trial will compare the efficacy of percutaneous transluminal coronary angioplasty (PTCA) with coronary artery bypass graft surgery (CABG) in patients with severe angina due to atherosclerotic narrowing of a coronary artery. Participants will be patients who are considered to be eligible for either procedure and who have multivessel coronary artery disease.

In the PTCA procedure, a catheter containing an inflatable balloon is introduced through a leg artery and guided under fluoroscopy to and through the narrowed section of the affected coronary artery. The balloon is then inflated briefly to dilate the narrowed portion of the artery and, thereby, improve blood flow. While CABG surgery is now quite successful and is presently the more widely accepted procedure, it involves surgery within the chest cage, a longer recuperative period, potential complications and greater costs. In contrast, PTCA involves no major surgery, has a quicker recovery, costs less, and is now associated with more success and fewer complications than in the past, but its long term results are less clearly defined. In the most experienced centers, successful dilation of coronary lesions has been obtained in over 90 percent of all PTCA patients, with a low rate of procedure related morbidity and less than a 1 percent operative mortality rate. Thus, it is essential to determine the comparative benefits and debits of these two therapies in terms of survival, symptomatic relief, morbidity and cost.

Duration: 8 years
First Year Cost: $1,000,000
Total Cost: $28,600,000

2. Dietary Intervention in Children with Elevated Low Density Lipoprotein Levels

Elevated levels of low density lipoprotein have been strongly implicated in the development of atherosclerosis. Increasingly, atherosclerosis is viewed as having its biological roots in early childhood. Preliminary findings indicate that a significant correlation exists between the levels of plasma LDL-cholesterol during childhood and early atherosclerosis in young adulthood. Further, there is an increased probability that a significant proportion of children in the upper decile of the plasma cholesterol distribution for their ages are at high risk for arteriosclerotic disease in adulthood. Research also indicates that dietary habits asociated with the development of elevated blood cholesterol levels are established early in life.

This clinical trial will assess the feasibility, acceptance, efficacy, and safety of dietary intervention in children to reduce plasma cholesterol levels. The primary measure will be the magnitude of reduction in the dietary intervention group as compared to the control group.

Duration: 7 years
First Year Cost: $700,000
Total Cost: $9,255,000

3. Treatment of Pulmonary Embolism with Thrombolytic Agents

An estimated 600,000 cases of pulmonary thromboembolism occur each year in the United States. Pulmonary thromboemboli are reported as the direct cause of 100,000 deaths a year and a contributing cause in an additional 100,000 deaths. While mortality is reduced among patients who receive heparin as an anticoagulant therapy, there is reason to believe that mortality could be further reduced by administration of one of the newly available thrombolytic agents, such as tissue plasminogen activator (tPA). Preliminary studies suggest that tPA administration may be an effective approach to dissolving blood clots that entails minimal adverse side effects such as bleeding. This study is designed to compare the effectiveness of thrombolytic therapy plus heparin with heparin alone in the treatment for pulmonary embolism. The two therapies will be compared on the basis of mortality, days of hospitalizaton, and days on anticoagulant therapy.

Duration: 5 years
First Year Cost: $1,000,000
Total Cost: $10,000,000

4. Continuous Positive Airway Pressure for Treatment of Sleep Apnea

Inadequate ventilation during sleep due to shallow, obstructed or erratic breathing--the sleep apnea syndrome--is estimated to affect 1 to 3 percent of the adult population of the United States. With inadequate ventilation during much of the night, body tissues tend to receive insufficient supplies of oxygen. Sleep is relatively restless, and those who suffer from the syndrome experience excessive daytime sleepiness and a diminished quality of life. Further, some 60 to 80 percent have hypertension.

Several therapeutic approaches are currently available, but each has its limitations. One recently developed treatment strategy that appears to hold promise is the administration during sleep of continuous positive pressure to the upper airways. The advocates of this therapy contend that it produces marked symptomatic improvement, is easily administered at home without serious side-effects and is accepted by patients. However, to date, there are no well-controlled clinical studies that have tested the approach, and it becomes important to assess the therapy before it becomes widely accepted without objective evaluation. The Institute is considering a multicenter study for such an objective assessment.

Duration: 6 years
First Year Cost: $800,000
Total Cost: $4,000,000

5. Penicillin Prophylaxis in Sickle Cell Disease

Children with sickle cell anemia have an increased susceptibility to fulminant bacterial infections that are a major cause of morbidity and mortality. Bacterial meningitis is 300 times as common in children with sickle cell disease as in the general pediatric population. Most such infections are due to the pneumococcus and occur before age 3.

Recent NHLBI studies have demonstrated that in young children, a regimen of prophylactic penicillin combined with pneumococcal vaccination reduces septicemia by about 90 percent. However, an important question remains. Must sickle cell patients be committed to a lifetime of prophylactic penicillin therapy or can it be stopped at a young age, such as 5? This clinical trial is designed to answer that question.

Duration: 2 years
First Year Cost: $900,000
Total Cost: $1,800,000

6. Natural History of Post-transfusion NANB Hepatitis

Post-transfusion hepatitis continues to be a significant transfusion associated risk, with 7 to 10 percent of all persons transfused developing the disorder. The majority of such cases are ascribed to non-A, non-B (NANB) hepatitis. The causative viral agent or agents for NANB hepatitis have yet to be identified. A retrovirus that may be the cause of NANB has been described recently, and the description needs to be confirmed. The long term consequences of NANB hepatitis virus infection, such as chronic hepatitis and cirrhosis, may be very important, but are not yet well defined.

This study proposes to identify patients in previous post-transfusion hepatitis studies. Those who developed chronic NANB hepatitis will be compared with those who did not develop hepatitis (control group). Reevaluation and further follow-up are planned.

Duration: 4 years
First Year Cost: $1,000,000
Total Cost: $3,215,000

7. Deep Vein Thrombosis Diagnosis and Treatment

In the late 1970s, the American Heart Association estimated the annual number of patients hospitalized with venous thromboembolism at 300,000. They also estimated that more than 50,000 of these patients die -- usually in hospitals, rehabilitation centers, and nursing homes.

A recent NIH consensus development conference concluded that venography, impedance plethysmography (especially combined with 125-I fibrinogen leg scans), and Doppler ultrasonography are the best available procedures for identifying the presence of deep vein thrombosis (DVT). Preliminary results from three surveys of medical practices relating to the diagnosis of DVT indicate disparate patterns of acceptance and use of diagnostic procedures. There is also a severe need for education in treatment modalities for DVT patients. It is essential that physicians become familiar with recommended treatment regimens for patients with DVT and with the potential adverse consequences of inappropriate treatment.

This initiative proposes to: 1) measure baseline information on the use and adequacy of current diagnostic methods and treatment modalities; 2) develop and implement an education program; 3) measure changes in physicians' use of these methods and modalities; and 4) measure changes in patient outcome.

Duration: 5 years
First Year Cost: $600,000
Total Cost: $10,800,000

8. Post Coronary Artery Bypass Graft Program

An estimated 200,000 patients received coronary artery bypass graft (CABG) surgery in 1984. The annual number of CABG procedures performed has increased every year since the technique was introduced and the trend is likely to continue. The mortality rate after successful CABG surgery varies between 1 and 5 percent per year depending on factors such as the severity of the underlying disease and the degree of existing ventricular dysfunction. Following the surgery, vessels close to the grafts may demonstrate accelerated atherosclerosis and the grafts themselves may progressively develop obstruction due to graft atheroma and fibrosis.

Further, it has been demonstrated that 15 percent of patients with preoperative angina have recurrent angina the first year after surgery and that an additional 6 percent develop the condition each subsequent year. Since reoperation has a higher operative mortality risk and less impressive benefit, it is important to develop effective methods of preventing postoperative occlusion and atherosclerosis.

Except for two trials that administered aspirin to CABG patients, there have been no studies to evaluate therapeutic intervention designed to reduce or prevent graft closure. This study will consist of two parts. One part is observational and will attempt to 1) clarify factors that initiate or facilitate coronary artery graft narrowing and occlusion, and 2) identify psychosocial variables that may influence CABG recovery. The major part is a clinical trial to determine whether lowering serum cholesterol by potent drug therapy or by life style modification provides beneficial effects to post-CABG patients.

Duration: 5 years
First Year Cost: $850,000
Total Cost: $29,500,000

9. Postmenopausal Estrogen Use and CHD Risk

The risk of coronary heart disease (CHD) in women increases over the postmenopausal years. In fact, heart disease is responsible for one-third of all deaths among women aged 50 to 69.

At present, the effect of estrogen on morbidity and mortality of coronary heart disease and the other effects of postmenopausal estrogen use are subjects of controversy. However, analysis of the Institute's Lipid Research Clinics' Follow-Up Study population suggests that such use of estrogen may have a profoundly beneficial effect on coronary heart disease.

The trial will assess the effects of varied estrogen and estrogen-progesterone combinations upon risk factors for coronary heart disease such as lipids, lipoproteins, and blood pressure, and upon such other important physiological features as bone density, the tissue lining the uterus, and certain endocrine functions. The goal is the identification of the presumably most favorable estrogen and estrogen-progesterone combinations from a comprehensive perspective.

Duration: 3 years
First Year Cost: $4,000,000
Total Cost: $12,700,000

RESEARCH INITIATIVES

Mr. Early. Will this budget request enable NHLBI to undertake any new initiatives?

Dr. Lenfant. Yes, the 1987 budget will permit the Institute to fund a number of initiatives supported by research project grants.

CENTERS

Mr. Early. Doctor, going back to the subject of research centers--in the past, when you've had reductions in direct costs, what has been the effect?

Dr. Lenfant. In the past, we have not had to reduce the direct costs of research center grants any more than 4 or 5 percent. These reductions have been achieved primarily by reducing costs for equipment, supplies, and purchased services, and have not had a major adverse impacts on the centers program. At the FY 1987 request level, however, center grants would be reduced approximately 16 percent from their approved levels. This degree of reduction would require reducing the size and scope of center projects, or reducing the number of centers.

Mr. Early. Are research teams disbanded?

Dr. Lenfant. Reductions in centers budgets which were smaller, did not required disbanding of research teams. Certainly, adjustments will have to be made. These adjustments will probably affect the size of research teams as well as the skills the team brings to the research.

Mr. Early. Are projects that are postponed or temporarily scaled back resumed?

Dr. Lenfant. Our past experience indicates that a few projects are eventually resumed as savings appear during the course of the research. However, the reductions proposed by the FY 1987 request have a much broader impact than past reductions.

BUDGET INCREASES

Mr. Early. If an increase over the FY 87 request is provided, how would you use these additional funds?

Dr. Lenfant. Should additional funds become available, the Institute would provide increased support to research centers and research contracts, the mechanisms that support much of our clinical trials and population based studies. The Institute would also restore reductions to the intramural research program so that ongoing research projects can continue. Should sufficient funds become available, the Institute would propose less drastic negotiation levels in research project grants.

INITIATIVES DELAYED

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed by lack of funds in the FY 87 budget?

Dr. Lenfant. Yes, initiatives or opportunities will be delayed.

Mr. Early. Please provide for the record, a list of these along with a brief description and the funding requirements associated with each.

Dr. Lenfant. We are now in the process of assessing and ordering initiatives for FY 1987, so the following must be considered a best projection rather than a definitive listing.

Initiatives include clinical, epidemiological and laboratory research, as well as clinical trials. The nine important clinical trial initiatives that will have to be deferred or delayed have already been summarized in response to a previous question. The following are additional research initiatives that will be deferred or delayed in FY 1987:

10. Effects of Dietary Fat on Lipoprotein Structure and Metabolism

Blood lipoproteins, as well as cholesterol, are known to be importantly involved in atherogenesis. Dietary fat is known to affect serum cholesterol and lipoproteins, but the interrelationships are inadequately understood. This research, which is to be conducted in metabolic wards in persons with moderate and high risk levels of blood cholesterol, will assess long-term effects and interrelationships of various modifications in dietary fats upon the levels and metabolism of the plasma lipoproteins including their subfractions and on other atherogenetic risk factor parameters. The ultimate goal will be to determine the most effective level of dietary fat and its components for achieving optimally balanced levels of lipoproteins and other coronary heart disease risk factor parameters.

Duration: 5 years
First Year Cost: $3,000,000
Total Cost: $18,000,000

11. Omega-3 Fatty Acids and Reduction of the Incidence of Thrombosis and Coronary Heart Disease

A low incidence of thrombosis and coronary heart disease has been noted among certain populations; e.g., Greenland Eskimos and Japanese fishermen. It has been suggested that the low incidence of such diseases is related to their unusual diet which has traditionally consisted of seal, whale, and fish. These seafood products have an unusually high content of polyunsaturated omega-3 fatty acids. Studies would be undertaken to determine the underlying basic mechanisms by which omega-3 fatty acids affect thrombosis and coronary heart disease.

Duration: 5 years
First Year Cost: $1,800,000
Total Cost: $16,800,000

12. Hypertension in Pregnancy--Population at Risk and Treatment

Blood pressure elevation is common in pregnancy. It is associated with 25,000 still births and neonatal deaths and 300 maternal deaths annually; it may also be the first step in the development or acceleration of persistent hypertension with its unfortunate complications. The research program would support studies on the etiology and pathophysiology of the condition, characterize the populations at risk, and study the effects of antihypertensive medications upon mother and fetus.

Duration: 5 years
First Year Cost: $1,000,000
Total Cost: $6,000,000

13. Mechanism of Obesity-Associated Hypertension

Obesity is associated with hypertension and in some instances predisposes to its development. Research in the fields of obesity and hypertension suggests that there are a number of weight and blood pressure regulatory systems. The objective of this research program is to elucidate the underlying mechanism(s) of obesity-associated hypertension in the hope that a path to improved control or prevention may be disclosed. Considering that obesity is also linked to coronary heart disease and diabetes, the knowledge gained from this research would provide additional benefits.

Duration: 5 years
First Year Cost: $2,000,000
Total Cost: $12,000,000

14. Laser Applications in Cardiovascular Treatment

Laser energy can be conducted along a fiber optical system within a catheter that is advanced in the arterial system to a site of obstruction or other disease. The laser energy can ablate and cut the tissue it hits with great precision. Optimal laser characteristics and energy delivery to ensure correct cutting without excessive penetration or local damage has yet to be defined. The research would focus on laser effects upon vascular tissue and upon the definition of optimal laser qualities for such applications as the ablation of occlusions (angioplasty), arterial welding, ablation of heart muscle for the control of certain arrhythmias, and perhaps valvuloplasty.

Duration: 5 years
First Year Cost: $2,500,000
Total Cost: $15,000,000

15. Minimally Invasive Techniques to Detect Coronary Artery Lesions

Detecting, locating, and measuring the degree of narrowing in coronary arteries is essential in the clinical management of persons with coronary heart disease. Presently, coronary angiography is needed, a procedure that requires the threading of a catheter from a peripheral artery back toward the heart and into the each of the two major coronary arteries with the subsequent injection of a "dye" which shows up on x-ray. The replacement of this invasive technique by an equally accurate non-invasive technique would enhance the ease and safety of the diagnostic procedure and probably reduce its cost substantially. There is promising research with digital substraction angiography using intravenously injected dye and with magnetic resonance imaging, both non-invasive techniques. Further work developing these technologies and with potential new technologies are needed to solve this challenging program.

Duration: 5 years
First Year Cost: $2,500,000
Total Cost: $15,000,000

16. Narrowing and Occlusion of Natural and Synthetic Grafts

Grafts are extensively used in peripheral vascular and heart surgery to bypass severely narrowed or occluded arteries. Both naturally occurring vessels and synthetic vessels are used for grafts. Unfortunately, grafts have a propensity for occlusion, particularly grafts involving smaller vessels. Research would focus upon the mechanisms involved in the occlusion of natural and synthetic blood vessel grafts used in leg artery reconstruction; it would also be of relevance for bypass grafting of the coronary arteries and of the carotid arteries leading to the brain.

Duration: 5 years
First Year Cost: $1,000,000
Total Cost: $6,000,000

17. Coronary Heart Disease and Stroke in the Elderly

Much more is known about the risk factors and mechanisms of "premature" heart and vascular disease occurring in middle-age than that occurring in the elderly. Objectives of this program are to assess risk factors predicting coronary heart disease and stroke in elderly men and women; proximate and long-term precipitants of new heart attacks, other coronary events, and stroke; and the predictors of mortality, chronic disability, functional impairment, institutionalization and survival among elderly patients with clinical coronary heart disease or stroke.

Duration: 6 years
First Year Cost: $2,500,000
Total Cost: $19,400,000

18. Coronary Heart Disease Care-Seeking Experience Among Blacks

Death due to coronary heart disease occurs at a higher rate in blacks than in caucasians. However, hospitalization for coronary heart disease in blacks is relatively less common. The objective of this research is to identify current concepts, beliefs, and behavior among blacks regarding the symptoms of coronary heart disease and the environmental factors and barriers that may influence their seeking and obtaining appropriate medical care. A related objective is to identify those health care provider factors that may influence the use of the medical care system, on the determination of diagnosis of acute coronary heart disease in minority patients, and upon the choice of treatment recommended and implemented.

Duration: 4 years
First Year Cost: $1,200,000
Total Cost: $8,800,000

19. Congenital Heart, Lung, and Blood Malformation Program

Congenital malformations of the heart are found in about 9 out of 1,000 newborn. Certain forms seem to be relatively constant in their incidence while others have changed importantly. Most congenital disease is of unknown etiology, but some may be due to viral infection. For example, maternal rubella during the first trimester of pregnancy was a common cause of congenital heart and other defects until the incidence of rubella was drastically reduced by vaccination. The goal of this research is to stimulate epidemiological investigation on congenital heart and related pulmonary and hematological diseases. A coordinated multicenter study group will collaborate in studies of etiology, natural history, associated lesions and familial clustering of congenital heart, lung, and blood diseases.

Duration: 5 years
First Year Cost: $1,800,000
Total Cost: $6,800,000

20. The Development of Hemostatic Mechanisms in the Newborn

At all times, blood must maintain a delicate balance between its readiness to form a clot upon bleeding and its ability to spontaneously break up or lyse clots and microthrombi. Research is clarifying the maturation of several fundamental biological processes during the neonatal period, but little is known of the maturation of the hemostatic system of the newborn. This research would elucidate the molecular biology of the processes that regulate maturation of coagulation proteins in normal premature and full-term infants and in those with hemorrhagic and thrombotic diseases, and it would seek to establish causality between derrangement in coagulation factor development and the pathophysiology of these diseases.

Duration: 5 years
First Year Cost: $600,000
Total Cost: $3,600,000

Mr. Early. Doctor, will any significant research initiatives currently underway be halted or seriously delayed due to FY 87 funding levels?

Dr. Lenfant. Initiatives in both the extramural and intramural program will be affected. Within the intramural research programs, a number of ongoing research projects will be terminated. Other initiatives within the intramural program, and under each of the mechanisms of the extramural program, will be delayed. The impact upon a number of our clinical trials has already been summarized.

Mr. Early. To what extent will there be major reductions in the scope of ongoing or new initiatives because of the FY 87 funding levels? For the record, please provide a list of these along with a brief description and the amounts associated with each initiative.

Dr. Lenfant. Reductions in the scope of ongoing or new initiatives will occur under the proposed budget. The Institute is currently assessing initiatives to determine where modifications are possible. This process is not yet complete. The Institute has reviewed ongoing initiatives and has modified several contract programs. To continue these programs as previously planned would require approximately $14 million in FY 1987. However, the Institute believes it can accomplish a substantial number of the objectives of these studies within the funds available by revising procurement schedules, size of the study population and so forth.

Mr. Early: What is the implementation date for changes in indirect cost rates announced in the February 12, 1986 Federal Register for each major Department of the Government? Please provide a list or table displaying the implementaion dates.

Dr. Lenfant. The information you requested is not available at this time. It will be provided to the committee as soon as it becomes available.

TRANSFUSION MEDICINE

Mr. Porter. What are your future plans for continued support for transfusion medicine programs?

Dr. Lenfant. The NHLBI plans to continue to support the Specialized Centers of Research (SCOR) and the National Research and Demonstration Center in Transfusion Medicine. These centers of excellence were established to expedite the development and application of new knowledge to ensure an adequate supply of safe and effective blood and blood products. Also, the Institute will continue its support of the Transfusion Medicine Academic Award program. This program encourages medical schools to develop curricula in the discipline of transfusion medicine and to further the development of skilled personnel who can serve the research, teaching, and clinical needs of transfusion medicine. In addition, the Institute will continue to develop and implement targeted research initiatives in areas of transfusion medicine where there is demonstrated scientific need. It will continue to grant training and career development awards in transfusion medicine for people to develop skills in this important scientific area. Finally, the Institute will continue to provide technical assistance to investigators as an aid to improving the quality of transfusion medicine applications.

Mr. Porter. Do you currently have the resources to increase investment in transfusion medicine research?

Dr. Lenfant. In FY 1985, the NHLBI devoted approximately $21 million of its budget to research activities related to transfusion medicine. Based on the funds available to the Institute, this area will probably not increase.

Mr. Porter. Do you feel that further investment in this area is appropriate? Do you think this should be a priority?

Dr. Lenfant. There are many opportunities for research emerging in the area of transfusion medicine. Furthermore, a critical mass of interested scientists has surfaced in recent years, and technology applicable to the problems of transfusion medicine has been developed. Because of the relation of blood safety to the use of blood and blood products, an increased effort directed to solving such problems as AIDS and transfusion related hepatitis must be seriously considered in any overall discussion of scientific priorities.

Mr. Porter. What are your recommendations regarding transfusion medicine and the relative importance of transfusion medicine among the various projects at NHLBI?

Dr. Lenfant. Transfusion medicine is a valid scientific discipline that has emerged in recent years. A cadre of highly trained investigators are pursuing a variety of scientific problems related to this area. There has been a surge of activity in recent years resulting, in part, from the emergence of sophisticated technology and the creation of a significant number of centers of excellence where important problems can be addressed. In this environment, one is able to explore many scientific questions that confront the field and to seize opportunities for progress in understanding, dealing with, and treating a number of diseases. Disorders treated with blood or blood products cause numerous days of hospitalization, cost countless dollars for health care, and lead to prolonged disability or suffering. Consequently, there are compelling reasons for pursuing such activities at the NHLBI.

Mr. Porter. With the amount appropriated for NHLBI, do you have the flexibility to meet needs as they arise?

Dr. Lenfant. Our flexibility to meet needs as they arise is today considerably less than it was in the past. The appropriated categories, such as heart and vascular diseases, lung diseases, blood diseases and resources, intramural research and research management and support, are now also subdivided along another axis by a new apportionment process that makes changes more difficult. There seems to be a greater reluctance to authorize revisions of these varied funding categories. In my professional judgment, I believe I could do a better job with a little more flexibility.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

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NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

For carrying out section 301, title IV, and [title XI] *Section 1105* of the Public Health Service Act with respect to cardiovascular, lung, and blood diseases, and blood and blood products, [$859,572,000] *$785,697,000. (Department of Health and Human Services Appropriation Act, 1986).*

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Amounts Available for Obligation 1/ 2/

	1985	1986	1987
Appropriation	$805,269,000	$859,572,000	$785,697,000
Enacted administrative reduction	---	-333,000	---
Sequester order	---	-36,947,000	---
Proposed rescission	---	-11,469,000	---
Subtotal, adjusted appropriation	805,269,000	810,823,000	785,697,000
Comparative transfer to:			
Office of the Assistant Secretary for Health, for AIDS Projects	-9,323,000	-10,718,000 2/	---
Subtotal, adjusted budget authority	795,946,000	800,105,000	785,697,000
Unobligated balance, start of year	---	639,000	---
Unobligated balance, end of year	-639,000	---	---
Unobligated balance, lapsing	-820,000	-669,000	---
Total obligations	794,487,000	800,075,000	785,697,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1985 - $263,000; 1986 - $150,000; 1987 - $17,461,000; of which $17,311,000 is for AIDS projects.

2/ The comparable amount for the appropriation is $11,200,000.

National Heart, Lung, and Blood Institute

Budget Mechanism
(Dollars in thousands)

	1986 Appropriation 1/2/		1986 Available After Sequestering 1/3/		1986 Revised 1/3/		1987	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research grants:								
Research projects								
Noncompeting..................	1,818	$369,412	1,818	$353,528	1,818	$353,528	1,803	$352,109
Admin. supplemental...........	(35)	1,162	(35)	1,112	(35)	1,112	(35)	1,162
Competing								
Renewal......................	296	67,510	296	63,830	264	58,261	269	61,028
New..........................	567	91,130	567	87,960	530	82,116	516	81,886
Supplemental.................	23	3,738	23	3,633	23	3,577	17	2,721
Subtotal, competing.............	886	162,378	886	155,423	817	143,954	802	145,635
Carryover....................	(1)	(639)	(1)	(639)	(1)	(639)	---	---
Subtotal, research projects....	2,704	532,952	2,704	510,063	2,635	498,594	2,605	498,906
Research Centers								
Specialized/comprehensive ctrs.	60	86,535	60	82,814	60	82,814	60	75,757
Other research								
Research career program........	364	22,915	364	21,930	364	21,930	364	21,906
Cooperative clinical research..	16	1,142	16	1,093	16	1,093	16	1,035
Minority biomedical research...	---	2,500	---	2,392	---	2,392	---	2,267
Other research related.........	55	9,159	55	8,766	55	8,766	55	8,489
Subtotal, other research.........	435	35,716	435	34,181	435	34,181	435	33,697
Total, research grants.............	3,199	655,203	3,199	627,058	3,130	615,589	3,100	608,360

	1986 Appropriation 1/2/		1986 Available After Sequestering 1/3/		1986 Revised 1/3/		1987	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Training								
Individual awards:								
Noncompeting	128	3,264	113	2,944	113	2,944	101	2,368
Competing								
Renewal	4	102	4	102	4	102	4	102
New	102	2,665	100	2,726	100	2,726	98	2,670
Subtotal, individual	234	6,031	217	5,772	217	5,772	203	5,140
Institutional awards:								
Noncompeting	1,296	29,762	1,230	28,292	1,230	28,292	1,200	25,938
Competing								
Renewal	130	3,130	130	3,130	130	3,130	63	1,781
New	50	1,283	50	1,283	50	1,283	34	910
Subtotal, institutional	1,476	34,175	1,410	32,705	1,410	32,705	1,297	28,629
Total, training	1,710	40,206	1,627	38,477	1,627	38,477	1,500	33,769
Research & development contracts	189	53,080	189	50,797	189	50,797	189	51,919
Construction		3,300		3,158		3,158		---
					FTEs		FTEs	
Intramural research		60,790		58,150	412	58,150	412	56,065
Research management & support		36,099		33,904	406	33,904	406	35,584
Total, NHLBI		848,678		811,544	818	800,075	818	785,697

1/ Reflects an enacted administrative reduction of $333,000 and a carryover in unobligated funds of $639,000.

2/ Reflects a comparable transfer of $11,200,000 to the Office of the Assistant Secretary for Health for AIDS projects.

3/ Reflects a consultant services (Section 515 of the Treasury-Postal Service Appropriation Act, 1985) withholding of $669,000 and a comparable transfer of $10,718,000 to the Office of the Assistant Secretary for Health for AIDS projects.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

CROSSWALK - 1986 Appropriation

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM									
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management Support	Construction	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional					
Heart and vascular diseases program........	$360,291	$42,535	$21,790	$4,565	$20,785	$43,770				$493,736
Lung diseases program...........	91,404	21,683	8,457	580	8,293	6,310				136,727
Blood diseases and resources program...........	81,257	22,317	5,469	886	5,097	3,000				118,026
Intramural research..........							$60,790			60,790
Research management and support.......								$36,099		36,099
Construction........									$3,300	3,300
Total...........	532,952	86,535	35,716	6,031	34,175	53,080	60,790	36,099	3,300	848,678

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

CROSSWALK - 1986 Available After Sequestering

(Dollars in thousands)

	MECHANISM									
	Research Grants			Training Programs						
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management Support	Construction	Total
Heart and vascular diseases program..	$345,064	$40,737	$20,869	$4,372	$19,907	$41,574				$472,523
Lung diseases program...........	87,480	20,791	8,095	555	7,937	5,994				130,852
Blood diseases and resources program...........	77,519	21,286	5,217	845	4,861	3,229				112,957
Intramural research..........							$58,150			58,150
Research management and support.......								$33,904		33,904
Construction........									$3,158	3,158
Total...........	510,063	82,814	34,181	5,772	32,705	50,797	58,150	33,904	3,158	811,544

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

CROSSWALK - 1986 Revised Estimate

(Dollars in thousands)

	MECHANISM									
	Research Grants			Training Programs						
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management Support	Construction	Total
Heart and vascular diseases program..	$337,610	$40,737	$20,869	$4,372	$19,907	$41,574				$465,069
Lung diseases program...........	85,416	20,791	8,095	555	7,937	5,994				128,788
Blood diseases and resources program...........	75,568	21,286	5,217	845	4,861	3,229				111,006
Intramural research..........							$58,150			58,150
Research management and support.......								$33,904		33,904
Construction........									$3,158	3,158
Total...........	498,594	82,814	34,181	5,772	32,705	50,797	58,150	33,904	3,158	800,075

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

CROSSWALK - 1987 Congressional Justification

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM Research Grants Research Projects	 Research Centers	 Other Research	 Training Programs Individual	 Institutional	 Research and Development Contracts	 Intramural Research	 Research Management & Support	 Construction	 Total
Heart and vascular diseases program..	$338,920	$38,058	$19,770	$3,918	$17,425	$40,404				$458,495
Lung diseases program...........	85,310	17,820	8,433	518	7,249	7,654				126,984
Blood diseases and resources program...........	74,676	19,879	5,494	704	3,955	3,861				108,569
Intramural research..........							$56,065			56,065
Research management and support.......								$35,584		35,584
Construction........									---	---
Total...........	498,906	75,757	33,697	5,140	28,629	51,919	56,065	35,584	---	785,697

National Heart, Lung, and Blood Institute

Summary of Changes

1986 Current estimated obligations..........................	$800,075,000
1987 Estimated obligations................................	785,697,000
Net change......................................	-14,378,000

	1986 Base	Change from Base
Increases:		
A. Built-in:		
1. Within grade increase..........	$32,688,000	+$522,000
2. Federal Employees Compensation Fund increase................	121,000	+29,000
3. FTS rate increase..............	482,000	+23,000
4. Payment for centrally furnished services...........	43,812,000	+2,171,000
5. Unemployment compensation fund.	20	+174,000
6. Increased cost of laboratory supplies, materials and other expenses...............	25,554,000	+1,073,000
Subtotal............		+3,992,000
B. Program:		
1. Research projects:		
a. Noncompeting continuations converting from competing status....................	354,640,000	+118,365,000
b. Competing (new, renewals and supplementals)........	143,954,000	+145,635,000
2. Research centers:		
a. Noncompeting continuations converting from competing status....................	68,350,000	+10,391,000
b. Competing (new, renewals and supplementals)........	14,464,000	+30,098,000
3. Other research:		
a. Noncompeting continuations converting from competing status....................	27,577,000	+7,855,000
b. Competing (new, renewals and supplementals)........	6,604,000	+6,071,000

	1986 Base	Change from Base
4. Individual training awards:		
a. Noncompeting continuations converting from competing status....................	3,164,000	+2,120,000
b. Competing (new, renewals and supplementals)........	2,608,000	+2,060,000
5. Institutional training awards:		
a. Noncompeting continuations converting from competing status....................	28,825,000	+3,880,000
b. Competing (new, renewals and supplementals)........	3,880,000	+1,383,000
6. Research and development contracts:		
a. Continuations...............	50,797,000	+1,122,000
7. Research management and support:		
a. High blood pressure and cholesterol education programs........	980,000	+258,000
Subtotal............		+329,238,000
Total, increases...............		+333,230,000
Decreases:		
B. Program:		
1. Research projects:		
a. Noncompeting completed or converting to competing status....................	354,640,000	-119,734,000
b. Competing (completed or converting to noncompeting status)..................	143,954,000	-143,954,000
2. Research centers:		
a. Noncompeting completed or converting to competing status....................	68,350,000	-33,082,000
b. Competing (completed or converting to noncompeting status)..................	14,464,000	-14,464,000
3. Other research:		
a. Noncompeting completed or converting to competing status....................	25,577,000	-7,806,000
b. Competing (completed or converting to noncompeting status)..................	6,604,000	-6,604,000
4. Individual training awards:		
a. Noncompeting completed or converting to competing status....................	3,164,000	-2,204,000
b. Competing (completed or converting to noncompeting status)..................	2,608,000	-2,608,000

	1986 Base	Change from Base
5. Institutional training awards:		
a. Noncompeting completed or converting to competing status....................	28,825,000	-5,459,000
b. Competing (completed or converting to noncompeting status)..................	3,880,000	-3,880,000
7. Construction:		
a. New.........................	3,158,000	-3,158,000
9. Intramural Research:		
a. Selected program decreases in lower priority areas...	58,150,000	-4,655,000
Subtotal...........		-347,608,000
Total, decreases...............		-347,608,000
Total, net change....................		-14,378,000

National Heart, Lung, and Blood Institute

Budget Authority by Activity
(Dollars in thousands)

	1986 1/ Appropriation	1986 Available After 2/ Sequestering	1986 2/ Revised		1987	
	Amount	Amount	FTEs	Amount	FTEs	Amount
Heart and vascular diseases program...	$493,736	$472,523	---	$465,069	---	$458,495
Lung diseases program............	136,727	130,852	---	128,788	---	126,984
Blood diseases and resources program..	118,026	112,957	---	111,006	---	108,569
Construction.........	3,300	3,158	---	3,158	---	---
Intramural research..	60,790	58,150	412	58,150	412	56,065
Research management and support........	36,099	33,904	406	33,904	406	35,584
Total obligations....	848,678	811,544	818	800,075	818	785,697
Unobligated balance, start of year......	-639	-639	---	-639	---	---
Unobligated balance lapsing....	---	669	---	669	---	---
Total budget authority..........	848,039	811,574	818	800,105	818	785,697

NOTE: All 1986 columns reflect an enacted administrative reduction of $333,000.

1/ Reflects a comparable transfer of $11,200,000 to the Office of the Assistant Secretary for Health for AIDS projects.

2/ Reflects a comparable transfer of $10,718,000 to the Office of the Assistant Secretary for Health for AIDS projects.

National Heart, Lung, and Blood Institute

Obligations by Object

	1985 Actual	1986 Estimate	1987 Estimate
Total number of Full-time permanent positions	770	770	770
Total compensable work years:			
Full-time equivalent employment	852	823	823
Full-time equivalent of overtime and holiday pay	7	10	10
Average ES salary	$66,232	$62,920	$62,920
Average GS grade	9.14	9.14	9.14
Average GS salary	28,224	26,813	26,813
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	35,361	33,593	33,593
Average salary of ungraded positions	23,306	22,046	22,046
Personnel compensation:			
Permanent positions	$21,695,000	$21,411,000	$21,894,000
Positions other than permanent	5,437,000	5,437,000	5,437,000
Other personnel compensation	917,000	917,000	917,000
Special personnel services	866,000	866,000	866,000
Subtotal, personnel compensation	28,915,000	28,631,000	29,114,000
Personnel benefits	4,110,000	4,057,000	4,125,000
Benefits for former personnel	---	20,000	194,000
Travel and transportation of persons	1,071,000	1,053,000	990,000
Transportation of things	134,000	113,000	100,000
Rent, communications & utilities	2,604,000	2,234,000	2,000,000
Printing and reproduction	1,669,000	1,030,000	900,000

	1985 Actual	1986 Estimate	1987 Estimate
Other services:			
Project contracts....................	56,737,000	50,797,000	51,919,000
Centrally furnished services.........	32,535,000	32,802,000	34,493,000
Standard level user charge...........	1,022,000	1,010,000	1,089,000
Other................................	11,988,000	10,476,000	9,407,000
Supplies and materials.................	9,491,000	7,866,000	7,407,000
Equipment..............................	2,890,000	2,762,000	1,830,000
Grants, subsidies & contributions......	641,321,000	657,224,000	642,129,000
Total................................	794,487,000	800,075,000	785,697,000

National Heart, Lung, and Blood Institute

Significant Item in House Appropriations Committee Report

Item	Action taken or to be taken
1986 House Report	
1. "The Committee expects the Institute, to provide a special report on Hypertension Specialized Centers of Research, including a discussion of the feasibility of expanding these centers." (p. 43)	1. A special report on Hypertension Specialized Center of Research has been forwarded to the Committee.

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1986 Amount Authorized	1986 Revised	1987 Amount Authorized	1987 Budget Request
Research and Investigation........	Section 301	42§281	Indefinite	$761,628,000	Indefinite	$785,697,000
National Heart, Lung, and Blood Institute.......................	Title IV, Part B and Title XI	42§285b				
National Research Service Awards..	Section 487	42§288 ℓ-1	$244,000,000	38,477,000	260,000,000	1/
Total Budget Authority..........				800,105,000		785,697,000

1/ This training authority is shared with other research training programs of the National Institutes of Health; the Alcohol, Drug Abuse, and Mental Health Administration; and the Health Resources and Services Administration.

National Heart, Lung, and Blood Institute

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation [1]
1978	406,203,000	434,909,000	456,000,000	447,909,000
1979	453,944,000	485,192,000	485,192,000	510,134,000
1980	507,468,000	527,544,000	527,544,000	527,488,000
1981	539,146,000	560,264,000	565,264,000	549,693,000
1982	510,050,000 [2]	583,831,000	585,741,000	559,637,000
1983	577,143,000	620,947,000	624,542,000	623,057,000
1984	637,738,000	665,859,000 [3]	683,489,000 [3]	700,068,000
1985	718,852,000	764,135,000 [4]	807,149,000	795,946,000
1985 Proposed Rescission	-1,401,000			
1986	775,254,000	856,388,000 [5]	863,652,000	859,239,000
1986 Sequester	-36,947,000			
1986 Proposed Rescission	-11,469,000			
1987	785,697,000			

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[1] Reflects enacted supplementals, rescissions, and reappropriations.

[2] Reflects the September amendment; the original request was $579,602,000.

[3] Excludes $28,490,000 in NRSA training programs not considered.

[4] Excludes $27,999,000 in NRSA training programs requested but not considered.

[5] Excludes $40,206,000 in NRSA training programs not considered.

National Heart, Lung, and Blood Institute

Justification

	1986 Appropriation Amount	1986 Available After Sequestering Amount	1986 Revised FTEs	1986 Revised Amount	1987 FTEs	1987 Amount
Heart and vascular diseases program.......	$493,736,000	$472,523,000		$465,069,000		$458,495,000
Lung diseases program.......	136,727,000	130,852,000		128,788,000		126,984,000
Blood diseases and resources program.......	118,026,000	112,957,000		111,006,000		108,569,000
Construction..	3,300,000	3,158,000		3,158,000		---
Intramural research program.......	60,790,000	58,150,000	412	58,150,000	412	56,065,000
Research management and support...	36,099,000	33,904,000	406	33,904,000	406	35,584,000
Total.......	848,678,000	811,544,000	818	800,075,000	818	785,697,000

General Statement

The National Heart, Lung, and Blood Institute (NHLBI) provides leadership for a national program in diseases of the heart, blood vessels, lungs and blood, and in the uses of blood and the management of blood resources. It plans, fosters, and supports an integrated and coordinated program that includes investigations, clinical trials, and demonstration and education projects relating to the causes, diagnosis, treatment, and prevention of heart, blood vessel, lung, and blood diseases. The program also includes studies of the clinical uses of blood and all aspects of the management of blood resources. In addition, the Institute supports research training and career development in basic and clinical research relating to heart, blood vessel, lung, and blood diseases and transfusion medicine. This diverse and balanced approach is required because of the magnitude of the multiple disease problems addressed by the Institute and because of the uneveness of our knowledge about these diseases and the treatment of patients who have them.

The diseases within the mandate of the Institute have a major impact on the American people. Together, all cardiovascular, lung, and blood diseases accounted for 1,142,000 deaths in 1984, or 56 percent of all deaths, and $133 billion in economic costs in 1983, or 24 percent of the total economic cost of illness and premature death. This cost estimate comprises $59 billion in direct health expenditures, $26 billion in indirect costs of morbidity (lost productivity due to illness), and $48 billion in indirect costs of mortality (lost potential productivity due to premature death).

Cardiovascular, lung, and blood diseases account for 5 of the 10 leading causes of all deaths, 5 of the 10 leading causes of infant deaths, and 5 of the 10 leading chronic conditions causing limitation of activity. Cardiovascular diseases caused nearly one of every two deaths in 1984. Lung diseases, excluding lung cancer, caused an estimated 174,000 deaths in 1984. Blood-related disorders are frequently a contributing factor in the development of diseases that are fatal, such as coronary heart disease, and they also cause disabling and eventually fatal chronic diseases such as Cooley's anemia and sickle cell anemia.

Over the past 20 years, there have been significant declines in mortality for the cardiovascular and blood clotting diseases, but an increase in mortality from chronic obstructive pulmonary disease. The overall improvement in mortality from cardiovascular diseases is reflected in the rapid increase in life expectancy in recent years. The downward trend in mortality from these diseases has persisted for 19 of the last 21 years. The impact of this decline is substantial. The age-adjusted rate for all causes of death dropped from 757 deaths per 100,000 in 1963 to 547 per 100,000 in 1984, and 70 percent of this reduction is the result of the decline in the death rate for cardiovascular diseases.

Advances in basic research are among the reasons for these improvements. The development of new techniques and concepts in the neurosciences and molecular biology, for instance, is revolutionizing the focus of basic research as it pertains to diseases under the purview of the NHLBI, and is providing approaches for understanding how the central nervous system controls the heart and vascular systems. Researchers are concentrating on brain neurochemicals, including neurotransmitters, neuromodulators, neurohormones, and certain peptides. Whether delivered by direct contact or through the bloodstream, neurochemical signals from the brain are continually maintaining, balancing, and adapting metabolism and cell function throughout the body. The brain also functions as a processor of the information received from these chemical messengers for millions of the body's cells. Application of biochemical and cytochemical techniques to the understanding of brain function has given rise to the percept that all neurons communicate with one another. The release of locus-specific neurochemical agents such as neurotransmitters acts to modify an impulse transmitted from one neuron to another. An important advance has been the development of techniques for tracing networks of neural transmission, initially by identifying the products of nerve cell degeneration and more recently through tracing methods, which chart, in great detail, the cartography of the brain. These techniques are leading to an increased understanding of brain function with respect to control of the circulation (and respiration as well) through the system of neurons intermittently connected to the cerebral cortex, the subcortical structures, and the upper brain stem. It is now apparent, for instance, that the central nervous system regulates the amount and pattern of the discharge of neurons to the heart and blood vessels, couples the cardiovascular system to behavior, and controls the release of various peptide hormones that regulate circulation.

Knowledge continues to be acquired through the technology of magnetic resonance imaging (MRI), which can be used to monitor noninvasively the concentration, turnover, and transport of many important metabolites and ions. Information obtained by this technique has led scientists to a new hypothesis about cell respiration in the intact heart, brain, and kidney based on the delivery of reduced substrates to the mitochondria within these tissues. Information from MRI is also causing researchers to question several dogmas of energy metabolism. Results of research in the field of molecular hematology, already being applied in studies in primates, have brought scientists to the threshold of trying genetic therapy in humans.

The success of the Institute's conference series on Frontiers in Basic Sciences that Relate to Heart, Lung, and Blood Diseases continues to grow. The purpose of the series is to capitalize on and transfer the achieved progress in basic science disciplines to clinical research problems. The topic of the most recent symposium was "Perspectives in Endothelial Cell Biology," at which leading researchers and experts in the field presented their views on the present state of the science, the problems facing current understandings, and anticipated future developments in endothelial cell biology. This area of research is germane to the heart, lung, and blood programs of the Institute.

The Institute has an Office of Prevention, Education, and Control (OPEC) since the passage of the National Heart, Blood Vessel, Lung, and Blood Act of 1972. The office develops educational and informational materials about clinical applications of research results and administers a clearinghouse of scientific and technical information about heart, lung, and blood diseases for the public and for health practitioners. The priority of this office continues to be the expansion of programs in cholesterol education and smoking education, which are modeled after the highly successful National High Blood Pressure Education Program. The high blood pressure program is a classic example of the way in which the Institute acquires, tests, evaluates, applies, and disseminates scientific information. It is now being transferred to the National Cholesterol Education Program. By the early 1970's, prospective epidemiologic studies demonstrated that hypercholesterolemia is a risk factor for atherosclerotic coronary heart disease, and animal experiments showed that reduction of serum cholesterol can prevent or reverse atherosclerosis. To test the hypothesis in humans, the NHLBI initiated the Lipid Research Clinics Coronary Primary

Prevention Trial in 1973. From a screening of over 480,000 candidates, 3,806 men 35 to 59 years of age agreed to participate. They were followed for an average of 7.4 years. The results, announced in 1984, show that each 1 percent decrease in blood cholesterol can be expected to reduce heart attack risk by 2 percent. The Institute launched the National Cholesterol Education Program in November 1985 through cooperation and coordination with other Federal agencies, with state and local agencies, and with professional, voluntary, and community organizations and groups throughout the country. The mission of the program is to reduce U.S. mortality and morbidity from high cholesterol related coronary heart disease.

Overall Budget Policy

The 1987 budget request will provide $785,697,000 for the National Heart, Lung, and Blood Institute, a decrease of $14,378,000 from the 1986 revised estimate.

The request will provide a total of $498,906,000 for noncompeting and competing research project grants. This level will be achieved by limiting indirect cost and by negotiating direct costs downward. The request will support 802 competing project grants at an average cost of $181.6. This represents a 5.5 percent increase in direct costs over 1986 and a 15.6 percent reduction from full recommended levels. Historically, these reductions have averaged 3 to 4 percent. The request will support 1,803 noncompeting project grants at an average cost of $195.3. This represents a 2.8 percent increase in direct costs over 1986 and a 9.4 percent reduction from full commitment levels. Historically, these reductions have averaged 1 percent.

The request provides $75,757,000 for 60 research centers, a reduction of $7,057,000 from the 1986 estimate for the same number of centers. Downward negotiations of approximately 16 percent will be necessary. This compares with negotiated reductions of 10 percent in 1986.

In other research, the request will provide $33,697,000 to fund a total 435 research career grants, cooperative clinical research grants, Minority Biomedical Support grants, conference grants, and demonstration and education grants, compared to 435 grants in 1986 at $34,181,000.

In research training, the 1987 request will provide $33,769,000 for 1,500 individual and institutional full-time training positions, a reduction of 127 trainees and $4,708,000 from the 1986 estimate.

The 1987 request will provide $51,919,000 for 189 research and development contracts, the same number funded in 1986 for $50,797,000. The increase will permit major clinical studies to continue.

The request will provide $56,065,000 for intramural research, a reduction of $2,085,000 from the 1986 estimate of $58,150,000. This reduction will be achieved through savings in travel, supplies, equipment, and other services.

In research management and support, the request provides $35,584,000 compared to the 1986 estimate of $33,904,000. The increase will provide funds for high blood pressure and cholesterol education programs.

Program Accomplishments

Basic Research

The process of arteriosclerosis underlies most of the estimated 11 million coronary, cerebrovascular, and peripheral vascular diseases reported in 1984, which caused about 736,000 deaths that year. In arteriosclerosis of the coronary arteries, cholesterol-containing plaques limit the flow of blood; eventually a blood clot forms, obstructing the artery and causing a heart attack or stroke. Researchers in the basic sciences are rapidly acquiring information about the role of cholesterol in arteriosclerotic processes. The cholesterol is derived from particles called low density lipoproteins (LDL), which circulate in the bloodstream. The more LDL there is in the blood, the more rapidly atherosclerosis develops. LDL receptors, which are proteins located on the surface of the liver and other cells, bind LDL particles and extract them from the bloodstream. In a process called receptor-mediated endocytosis, the LDL is taken into the cells and broken down, where it yields its cholesterol to serve the cell's need. The process also removes LDL from the bloodstream. When a cell's need for cholesterol is low, the cell makes fewer receptors and takes up LDL at a reduced rate. As a result, cholesterol accumulates in the blood, LDL is removed from the blood at a reduced rate, the blood level of LDL increases, and atherosclerosis is accelerated. Also, if the receptors are defective, LDL is not removed normally and it accumulates to a high level. Approximately 1 person in 500 inherits a mutant gene altering the function of the receptor. A single copy of this gene produces heterozygous familial hypercholesterolemia, which is a common cause of heart attacks in middle-aged people. Genetically induced alterations in the LDL receptor are now the subject of research. Results should provide a wealth of information about the mechanism of receptor-mediated endocytosis and should suggest means of inhibiting the atherosclerotic process. The Nobel committee recognized the importance of this accomplishment by awarding the Nobel prize for medicine to Drs. Michael S. Brown and Joseph L. Goldstein, whose research on the LDL-receptor was supported by the Institute since the beginning of their research. For the same work, Drs. Brown and Goldstein also received the Albert Lasker Basic Medical Research Award.

As a result of basic research on pediatric lung diseases, it has been learned that infants born prematurely who develop respiratory distress syndrome (RDS) are deficient in a lipoprotein complex called pulmonary or lung surfactant. The complex is synthesized in certain lung cells and secreted into the air sacs. The substance reduces the surface tension of pulmonary fluids and thus greatly reduces the work of breathing. Results of studies suggest that proteins in lung surfactant enhance the movement of surfactant lipids to the alveolar surface. The entire sequence of amino acids in canine and human surfactant apoproteins has recently been determined. Together with calcium ions, this group of proteins has been shown to be essential for rapid surface tension lowering. In a related area, researchers have cloned the gene for the protein component of the human surfactant. Laboratory scientists can now synthesize large quantities of surfactant protein. These recent accomplishments will provide molecular probes for future studies to determine the structure and regulation of the gene or genes responsible for encoding surfactant protein. They also make it possible for investigators to study gene expression during lung development and to generate human surfactant-associated protein for possible clinical use. Further research will also help investigators to understand the function of the surfactant protein. If abnormalities of the surfactant gene are important in neonatal RDS, prenatal screening for infants at risk of developing the disease may be possible.

In the area of blood diseases, aplastic anemia encompasses a group of disorders with numerous etiologies and a variety of natural histories. It is a bone marrow abnormality characterized by significantly reduced amounts of two or more types of blood cells. The disease can be inherited, but more often it is acquired as a reaction to drugs, chemicals, toxins, radiation, or infections. Because of the complexity of the system that produces blood cells (hematopoiesis), it has been difficult to develop a basic understanding of the mechanisms responsible for bone marrow failure. The recent adaptation of a long-term murine bone marrow culture system to human marrow has provided an improved laboratory model of human hematopoiesis. An essential feature of this system is the development of a heterogeneous adherent layer of cells (functionally defined as stromal cells) and intercellular matrix. Hematopoietic stem cells reside in this layer, and if the metabolism of the layer is inhibited, stem cell proliferation is abrogated. This structure may be a laboratory counterpart of the human hematopoietic microenvironment for use in future studies. In a related area, stromal cells in long-term marrow cultures have been examined for responsiveness to platelet-derived growth factor (PDGF) and epidermal growth factor (EGF). Many stromal cells from cultures derived from normal donors as well as from patients with myelogenous leukemia bore receptors to PDGF and EGF. These data suggest that PDGF and EGF may have a function in the regulation of the experimental microenvironment and therefore of normal and abnormal human hematopoiesis. An additional promising development is that monoclonal antibodies are becoming available for investigating cell surface receptors. These various accomplishments will lead to a clearer understanding of, and more effective therapies for, the disease.

Applied Research

One of the principal problems in heart transplantation has been long-term support of the donor heart to provide more time for transportation. Available techniques allow only a few hours between the time of removal of the heart from the donor and the time of implantation. Increasing the number of donor organs will depend on improving the ability to maintain donor hearts in a viable state. Recently developed techniques may help achieve the ultimate goal of a heart organ bank. Continuous perfusion of the isolated heart with what has been called a "physiologically complete" medium results in significantly increased levels of high energy phosphates. The ventricular performance of these hearts is far better than that of hearts preserved by the standard techniques presently employed for clinical cardiac transplantation. This accomplishment should lead to longer preservation and viability of donor organs.

The technique called balloon angioplasty has been used to overcome blockage of the coronary arteries by atherosclerotic lesions, which can cause angina or heart attack. Diseased coronary arteries are widened by inflation of a small balloon located at the tip of a catheter, which is introduced directly into the site of blockage. A possible alternative to this method is to remove plaque at the site of blockage by the use of a laser incorporated into the catheter. In a series of experiments using fresh human postmortem coronary arteries, a variety of different laser types has now been studied. The short-pulse carbon dioxide and the eximer lasers show excellent results and minimal associated tissue injury. These lasers are the subject of further studies.

Recent applied research on sleep apneas also promises important results. During sleep, the activity of the muscles that dilate the upper airway during inspiration decrease more than diaphragm activity decreases. Resulting differences in pressure tend to collapse the upper airway enough to block air flow. Pharmacologic agents that stimulate respiration have been used for obstructive apneas in sleep, but results have varied. A drug designed to alter the mechanisms involved in the nerves supplying the upper airway muscles could be of use in reducing the occurrence of obstruction during sleep. Recent studies of anesthetized and of conscious animals have demonstrated that nicotine excites upper airway muscles more than it excites the diaphragm. Nicotine given in the form of chewing gum to patients with sleep apnea syndrome had no effect on carbon dioxide or oxygen levels during wakefulness or on breathing patterns during sleep. Nicotine decreased the total number of apneas during sleep and reduced the total time spent in apnea during sleep. Cigarette smoking, however, has been associated with difficulties in sleeping, and in its present form, nicotine is probably not the best therapeutic agent for obstructive sleep apnea. Additional studies are needed to develop drugs that have longer lasting upper airway stimulating effects but that do not interfere with sleep.

Many diseases might be effectively treated if genes could be transferred into, and expressed in, bone marrow cells. In sickle cell disease and in the thalassemias, it might be possible to correct the defect if functional genes could be introduced into bone marrow cells of such patients. Recent developments make this a potentially achievable goal. Certain viruses infect bone marrow cells. The genetic information contained in these viruses becomes part of the genetic repertoire of the infected cells. Murine bone marrow cells have been infected with such viruses, carrying transferred genes. The blood-forming cells in these animals have been shown subsequently to contain the new and appropriately expressed genetic information. Before the full promise of these experiments is realized, studies of a well-characterized animal model, with similarities to humans, will be necessary.

To date, no truly effective, nontoxic treatment for preventing or alleviating the clinical manifestations of sickle cell disease has been found. A variety of promising pharmacologic approaches have been suggested, but thus far, none has produced a clinically useful drug for long-term treatment. Many of the symptoms of sickle cell disease are caused by the gelation, or clumping, of the sickle hemoglobin in the red blood cell when oxygen is released to the tissues. Prevention of gelation might be accomplished by a "designer" pharmacologic agent whose structure interferes with sickle hemoglobin polymerization. This stereospecific approach involves the careful selection of structurally specific compounds that interfere with intermolecular contacts in the deoxyhemoglobin S polymer or that decrease the effective concentration of the deoxycompound. Investigators working collaboratively have used x-ray crystallography to determine the binding sites of two very potent antisickling agents. These studies have suggested possible molecular mechanisms of action for the antisickling properties of these drugs.

Technology Development

A working group on mechanical circulatory support, which was established in 1983 by the Director, NHLBI, and included experts in cardiology, cardiovascular surgery, biomedical engineering, medical ethics, health policy, health economics, and medical social work, reviewed the state of knowledge about implantable artificial hearts, the potential need for such devices, their cost, and certain societal and ethical issues related to their use. The group, which reported in May 1985 to the National Heart, Lung, and Blood National Advisory Council, concluded that effective and safe mechanical circulatory support systems, reliable for periods of several years, are feasible. In addition, they agreed that effective, fully implantable, long-term artificial hearts could provide a significant increase in lifespan for patients below age 70, with an acceptable quality of life for 17,000 to 35,000 persons annually. They estimated that the costs per person for a device, its implantation, and its maintenance for a projected average of 4.5 years of survival would be approximately $150,000. Such a mechanical circulatory support system would cost about the same as aggressive treatment of neoplasms, burns, and other serious disorders. The working group concluded by recommending that research on mechanical circulatory support should continue and that the targeted program of fully implantable long-term ventricular assist devices should be continued. They further urged that the goal of a fully implantable, long-term, total artificial heart should be actively pursued.

A portable device that measures blood pressure during a patient's daily activities is proving to be an accurate predictor of hypertension-related illness. Such a device consists of a miniature motor that automatically inflates a blood pressure cuff, and a recorder that can store up to 300 readings for a period of up to 24 hours. However, costs range from $2,000 to $20,000, depending primarily on the mode and amount of data storage. A recently completed 5-year study of more than 1,000 patients demonstrated that the ambulatory monitoring was more reliable for predicting illness than single readings taken at a physician's office. Data that establish normal ranges for blood pressure during ambulatory monitoring are now being collected. These data will help define the precise role of the device in patient care.

Chronic obstructive pulmonary disease (COPD) caused 66,000 deaths in 1984 and is the fifth leading cause of death. Patients with advanced COPD often develop respiratory failure. This event necessitates mechanical ventilation, for which rapid determinations of respiratory system mechanics are needed to provide a sound basis for clinical management. A new test based on an interrupter technique consists of measurements of air flow, volume, and tracheal pressure during a series of very brief occlusions of the airway during a relaxed expiration. Previously thought to be inaccurate, the technique has recently been evaluated in groups of patients in acute respiratory failure with and without COPD. It allowed accurate determination of respiratory mechanics in both groups. The technique additionally allows for gathering quantitative information on respiratory system mechanics at the bedside. It may eventually be useful in predicting when a patient can discontinue ventilatory support. In addition, the data may help in predicting ultimate patient outcome.

Clinical Studies

Over the past several decades, interest in diet and cardiovascular disease has focused primarily on the relationship of sodium and obesity to hypertension. Evidence now beginning to accumulate suggests that a number of other dietary factors, such as potassium, calcium, proteins, amino acids, trace metals, carbohydrates, and fats, also exert effects on blood pressure. High potassium intake, for instance, is now associated with lower blood pressure. Conversely, a low potassium intake is possibly a contributing factor in essential hypertension. The sodium-potassium ratio in the diet may therefore be of vital importance in blood pressure control, and increases in potassium in the diet may be as beneficial as reductions in sodium intake. An inadequate intake of calcium may also be a factor in the development of hypertension. These hypotheses merit further study. There is also a growing interest in mechanisms of obesity-related hypertension. Blood pressure reduction accompanies weight loss in obese hypertensives, even when they are on a normal salt diet. Little research, however, has focused on the pathophysiology of obesity-related hypertension. Study of these various factors and their cardiovascular effects is important not only for their etiologic implications, but also for possible modulation of these nutrients in the treatment and prevention of hypertension.

Data from the Coronary Artery Surgery Study (CASS) continues to provide valuable information. The improved survival of patients with triple-vessel coronary artery disease and low ejection fraction following coronary bypass surgery has recently been reported. At 7 years, 84 percent of patients in the surgical group were alive, as compared with 70 percent of the medical group. Similar results have been independently reported from a randomized clinical trial conducted in Veterans Administration hospitals. These findings provide further clarification of the type of patients who may be benefited by elective coronary bypass surgery. In addition, advances in therapy for acute myocardial infarction and for symptomatic patients with coronary heart disease are being reinforced by studies at the more fundamental levels of the coronary arteries and of abnormalities associated with myocardial ischemia. The use of saphenous veins in aortocoronary bypass grafts has become a common surgical treatment for various forms of ischemic heart disease, and subsequent failure of the grafts is now being studied. Investigators have observed that endothelial cells from venous and arterial tissue differ in their pharmacological properties. This in fact is the first demonstration of pharmacological differences between venous and arterial endothelium, and this important observation may lead to improved methods of graft preparation and prolonged graft patency.

Although primary pulmonary hypertension (pulmonary hypertension of unknown etiology) is relatively uncommon, the study of this disease is important because it has a poor prognosis and is almost always fatal. Because no one sees enough patients to obtain sufficient data for statistical analysis, the Institute has established a national patient registry to collect data from 35 centers on patients with confirmed primary pulmonary hypertension. As of September 30, 1985, more than 300 cases were entered in the registry. This large number of patients will allow for better characterization and understanding of this disorder and should lead to new insights into the pathogenesis, natural history, and treatment of the disease.

The high rate of death caused by S. pneumoniae infections in infants and young children with sickle cell disease has led to a study of the effectiveness of prophylactic penicillin for such patients. In this study, which included 71 persons between 6 months and 5 years of age for a total period of 6.5 years, there were only 7 episodes of infection in 6 patients (or 3.4 episodes per 100 person-years), with 3 deaths. Although the study shows that absolute protection is not achieved and that strict compliance is necessary, it is clear that prophylactic penicillin reduces death associated with this infection.

Prevention

The Dietary Intervention Study in Hypertension, begun in 1980, enrolled 496 patients who had participated in the Hypertension Detection and Followup Program (HDFP) and whose blood pressure was controlled for up to 5 years by medication. The participants were randomized into groups with and without dietary intervention. Over a period of 56 weeks, the patients in the dietary intervention groups were more than twice as successful as those in the control groups in maintaining normal blood pressure. For the estimated 40 million Americans who are being treated for high blood pressure or have elevated diastolic blood pressure, this study has important implications. Many patients who adhere to dietary regimen to control blood pressure can reduce or stop drug therapy, with potential economic and health advantages. Long-term observations, however, are needed to ascertain whether these results are temporary.

The Honolulu Heart Program, which is an ongoing, long-range, prospective epidemiological study of biological and environmental causes of cardiovascular disease among American men of Japanese ancestry, continues to provide valuable information about coronary heart disease and stroke and to confirm the possibility that disease risk can be reduced by beneficial changes in diet and lifestyles. Data now show that men who developed coronary heart disease had a higher intake of protein, fat, and saturated and polyunsaturated fatty acids than men who remained free of coronary heart disease. Risk factors for thromboembolic stroke were elevated blood pressure, glucose intolerance, age, ECG evidence of left ventricular strain, cigarette smoking, and proteinuria.

Of the Institute's 15 school-based cardiovascular demonstration and education research studies of children, 3 have already reported results. Each report indicates that the program is achieving its goals. In the Chicago Heart Health Curriculum Program, more than 3,600 students in over 200 classrooms were involved. Results show substantial gains in knowledge and some beneficial changes in attitudes. The "Know Your Body Program," which involved 22 elementary schools in New York, was a 6-year longitudinal study of the feasibility and effectiveness of a strategy for primary prevention of coronary heart disease. After 3 years of intervention, results show that diastolic blood pressure levels decreased more among intervention subjects than among control subjects and that total cholesterol-HDL ratios decreased more among intervention subjects than among controls. In a study involving two Baltimore schools, students in the 9th and 10th grades had a blood pressure screening and were then randomly assigned to a relaxation group or to a delayed treatment control group, which would receive the relaxation treatment the following semester. Results show a decrease in systolic blood pressure levels in the relaxation group.

This wealth of valuable information about disease prevention and also about strategies for disease prevention programs has accumulated since the publication 5 years ago of the NHLBI *Cardiovascular Primer for the Workplace*. During the interval, the Institute has gained experience in developing successful disease prevention programs by facilitating the implementation of such efforts in businesses and organizations. In addition, the weight of the scientific evidence that a reduction of known risk factors reduces the prevalence of morbidity and mortality continues to grow. Drawing from this experience and incorporating the expanded knowledge about disease prevention, the Institute is completing an entirely new edition of the primer. Called *Heart Health at the Workplace: It's Your Business*, the booklet is designed to help business and organization executives, labor unions, and occupational health care professionals develop successful workplace programs to reduce disease risk.

In FY 1985, the Institute began recruiting participants for a randomized and controlled clinical trial on the Prevention of Chronic Obstructive Pulmonary Disease. Recruitment will continue through calendar 1986, and the intervention and followup will last 5 years. The sample will consist of 7,800 cigarette smokers between the ages of 35 and 54, drawn from the general population. Initially, the smokers will be screened for their level of pulmonary function. Of the subjects enrolled in the trial, 20 percent may be expected to show evidence of hyperreactive airways. Treatment of participants randomized to the special-care group will include smoking cessation counseling and diligent followup.

Thus, the Institute's program responds to the entire biomedical spectrum, from research to expand basic scientific knowledge to the development and evaluation of educational programs for the control and prevention of heart, lung, and blood diseases.

AIDS Research

The request excludes $17,311,000 for AIDS, which is under the single AIDS appropriation in the Office of the Assistant Secretary for Health. Comparable amounts for 1986 are $10,718,000 and for 1985 $9,323,000.

Within its overall mission, the Institute has responsibility for research on blood diseases, the use of blood products, and the management of blood resources. It is conducting AIDS research because it is now well established that HTLV-III, the causative agent of AIDS, can be transmitted by blood, blood components and blood derivatives. Of the 16,000 cases of AIDS reported in the United States as of December 30, 1985, one percent of adult cases occurred in hemophiliacs, and two percent are transfusion related.

The Institute supports several AIDS research projects. One is a major, multicenter study of immunologic alterations that occur following multiple blood transfusions and the possible association of these changes with the development of AIDS. The individuals being evaluated include HTLV-III antibody-positive blood donors, inadvertant recipients of HTLV-III positive blood (transfused before testing was available to the blood-banking community), patients with hemophilia (including their children, spouses or sexual partners), sickle cell disease patients and patients with thalassemia. Of immediate concern has been an evaluation of blood donors for antibody to HTLV-III in high prevalence areas. From early September, 1984, through early February, 1985, serum samples were collected from over 201,000 blood donors. These samples were taken before HTLV-III antibody testing was available. The sera are now being tested and the donors whose serum samples show the presence of antibody to HTLV-III are being asked to participate in a study to follow their immunologic and virologic status over a three-year period. Similarly, the recipients of blood from some of these HTLV-III antibody-positive donors are also being identified and enrolled into this prospective study. The study will attempt to answer several important questions regarding the transmission of HTLV-III by blood transfusion.

The current ELISA tests for screening blood donors are not entirely satisfactory. A synthetic peptide identical to glycoprotein 160 in the envelope of HTLV-III is under development. This peptide may lead to development of an improved assay for antibody to HTLV-III. The peptide could replace disrupted virus that is employed in commerical assays currently in use and could significantly reduce the false-positive rates that are presently being observed in blood banks around the country.

This same peptide is being evaluated as a possible candidate for a synthetic subunit vaccine. In fact, a significant first step toward the development of such a vaccine was taken when it was demonstrated that the synthetic peptide elicited an antibody response in rabbits and that these antibodies were specific for HTLV-III. A chimpanzee inoculated with the peptide also produced a significant antibody response. If the chimpanzee remains virus culture negative after challenge with the virus, this finding will be an important step toward the development of a synthetic vaccine for AIDS.

Investigators have recently developed a chemical procedure to inactivate HTLV-III in blood products which has potential application in the preparation of safe, effective blood derivatives. This treatment had little effect on the stability of factor VIII and thus may serve as an alternative to heat treatment of factor VIII, which has been shown to reduce the biological activity of the enzyme.

The Institute is supporting the development of an immune globulin which may prove useful in certain populations in preventing AIDS after exposure to the HTLV-III virus. Before its preparation is undertaken, it will be necessary to demonstrate whether neutralizing antibodies to HTLV-III exist in sera of patients with AIDS, and if so, in what quantities. Investigators are presently testing male homosexuals for such neutralizing antibodies to HTLV-III and that high-titer ad serum exist which might be utilized for an immune globulin preparation. An investigational product suitable for clinical use will be developed in accordance with FDA regulations and a controlled trial of its efficacy in humans would be recommended.

Appropriate animal models for AIDS are indispensable for assessing the clincal course of the disease, for determining safety and efficacy of therapeutic agents, and for confirming viral inactivation in blood products. The Institute supported the first study establishing the chimpanzee as an animal model for HTLV-III infection, the causative agent of AIDS. One of the infected animals that developed HTLV-III antibodies and severe lymphadenopathy has now clinically recovered, but continues to circulate antibodies to HTLV-III. Another animal, that was infected with HTLV-III but manifested no clinical immunologic evidence of AIDS, also continues to circulate antibody to HTLV-III. The investigators have recently succeeded in transmitting the virus from chimpanzee to chimpanzee. The incubation period of the virus in the newly infected chimpanzee was approximately 3 months. Investigators are currently examining factors that may contribute to the progression of HTLV-III infection from the asympbounatei state to overt AIDS.

The 1987 budget request will permit the Institute to support ongoing AIDS research, and to fund some new investigator-initiated research project grants. Areas that may receive future research support are studies of the pulmonary complications of AIDS, evaluation of current blood tests, the development of new blood tests, and the transmission of HTLV-III among household members of hemophiliacs carrying the virus.

National Heart, Lung, and Blood Institute

Heart and Vascular Diseases

1987 Authorization: Indefinite.

Obligational Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$493,736,000	$472,523,000	$465,069,000	$458,495,000	$ -6,574,000

Purpose and Method of Operations

Despite significant reductions in death rates over the past 21 years, cardiovascular diseases continue to rank high among the leading causes of death in the United States. The 978,000 deaths due to cardiovascular diseases in 1984 constituted nearly half of all deaths. An examination of the deaths by diagnosis shows a clear dominance of arteriosclerotic-related causes: coronary heart disease, 536,000 deaths (55 percent); stroke, 140,000 deaths (16 percent); and peripheral vascular disease, 46,000 (4 percent). Other cardiovascular diseases, including hypertension, cardiac failure, cardiomyopathies, infections of the heart, and arrhythmia, accounted for an additional 224,000 deaths in 1984.

Coronary heart disease is the major cause of death in men after age 40 and in women after age 50. The annual incidence of coronary attacks is estimated to be 1,250,000. The prevalence rates for most cardiovascular diseases increase markedly with age; coronary heart disease is more than twice as prevalent in the 65-and-over age group than in the 45 to 64 age group.

Black men and women continue to show marked differences in mortality from stroke and other heart disease compared to white men and women. In 1982, rates of death from stroke between the ages of 35 and 74 were more than twice as high in the black population than in the white population, and rates for coronary heart disease were almost twice as high for black women than for white women in the same age group. On the basis of recent findings, there is reason to believe that the differentials may be reduced by systematic, sustained management of blood pressure. The 5-year results of the Hypertension Detection and Followup Program (HDFP) showed reductions in all-cause mortality in the stepped-care treatment program of 18.5 percent among black men and 27.8 percent among black women when they were compared with the black participants in the referred care group.

According to data on the prevalence of heart and vascular diseases in the United States, more than 60 million persons have been diagnosed by their physicians as having hypertension, heart disease, or a circulatory disease. In 1982, an estimated 17 million persons had some form of heart disease: 5.6 million with coronary heart disease, 1.6 million with rheumatic heart disease, and 10 million with other forms of heart and vascular disease. More than 2 million persons were estimated to have cerebrovascular disease.

The total annual cost associated with cardiovascular diseases was estimated at $94 billion in 1982, by far the largest total for any diagnostic group of diseases. The direct costs alone (hospital care, physician and other professional services, drugs, and nursing home care) amounted to $41 billion, or 1 percent of the GNP. An additional $53 billion was lost to the economy in indirect costs (lost productivity and premature deaths). Coronary heart disease, which kills and disables people in their most productive years, accounted for $9.4 billion of the 1982 direct costs associated with cardiovascular disease. Coronary heart disease is also the leading cause of premature permanent disability in the American labor force, accounting for 19 percent of disability allowances by the Social Security Administration. To reduce the economic burden and the mortality and morbidity imposed on the Nation by cardiovascular disease, the Heart and Vascular Diseases Program will continue its emphasis on basic biomedical research, clinical applications of research, clinical trials, and prevention, education, and control programs. Ten program areas are emphasized, each representing a National Program category: arteriosclerosis, hypertension, cerebrovascular disease, coronary heart disease, peripheral vascular disease, arrhythmias, heart failure and shock, congenital and rheumatic heart disease, cardiomyopathies and infections of the heart, and circulatory assistance. Within these ten areas, major emphases is focused on arteriosclerosis, hypertension, and coronary heart disease programs.

The Heart and Vascular Diseases Program is responsible for developing and fostering programs that will encourage the scientific community to participate in the full-range of investigative opportunities available in basic and clinical research, clinical trials, applied and developmental research, and demonstration education research. In addition, the program encourages interest in selected areas of science or disease problems by soliciting research through request for applications (RFA), contract proposals (RFP), and program announcements.

The Heart and Vascular Diseases Program uses several mechanisms to support investigator-initiated and Institute-solicited research. Nearly 70 percent of the program's budget supports research project grants; 10 percent supports research centers; 10 percent supports career development, training, and other grant research; and 10 percent supports research contracts.

To support research activities, the program uses the traditional research project grant; the program project grant, for more broadly based multidisciplinary research; the new investigator research award, to assist newly trained investigators to gain independent research experience in basic and clinical studies during the developmental stages of their careers; and the small business innovative research grant, to establish the feasibility of biomedical research ideas for commercial use.

This program supports highly successful specialized centers of research (SCORs) in arteriosclerosis, hypertension, and ischemic heart diseases. By combining these with a demonstration and education research component, the Heart and Vascular Diseases Program has expanded these multidisciplinary basic and clinical research centers to include demonstration and education research to help assure prompt application of new knowledge to the prevention and treatment of cardiovascular diseases.

To assure a sufficient number of specially trained research scientists, the Heart and Vascular Diseases Program continues to support its research career efforts. Among these programs are the Research Career Awards, Clinical Investigator Awards, Preventive Cardiology Awards, and Physician Scientist Awards. In addition, the Heart and Vascular Diseases Program has sought to encourage minority institutions to apply for support through the new Institute-initiated Minority School Faculty Development Award. This program is designed to offer research support in cardiovascular diseases to minority school faculty members who have the interest and capability to perform modern, sophisticated research in these areas. Other minority support mechanisms for predoctoral and postdoctoral trainees include the NRSA Minority Programs for Hypertension.

Academic training for early predoctoral and postdoctoral individuals through the National Research Service Awards has provided trainees with the opportunity to broaden their scientific knowledge and thereby extend the potential for qualified researchers to advance in the health-related areas. This training has been expanded to include minority institutions through the Minority Institutional Research Training Program and the Research Fellow Program for Investigators at Minority Institutions. The institutional research training program is intended to train graduate students in minority schools that have the potential to develop a meritorious program in cardiovascular or other diseases relevant to the Institute's mission. This fellowship provides opportunities for investigators to acquire experience in the use of sophisticated technologies and laboratory techniques.

Contract-supported research has provided the means to acquire specific research which meets a predetermined program need. The Heart and Vascular Diseases Program uses research and development contracts largely to support large-scale clinical trials or for the development and acquisition of treatment devices such as the assist devices program. Clinical trials generally involve multiple centers and explore, prove, or disprove some form of treatment or patient management technique. As a result of these large scale trials, significant research advances in arteriosclerosis, hypertension, cerebrovascular disease, coronary heart disease, and peripheral vascular disease continue to be realized.

Rationale for the Budget Request

The 1987 budget request for the Heart and Vascular Diseases Program is $458,459,000, a decrease of $6,574,000 from the 1986 level of $465,069,000. This budget request permits progress toward long-term goals in a way that is consistent with the overall budget strategy of reducing the Federal deficit.

There has been considerable progress to date as shown by the following examples of recent accomplishments and future plans in basic and clinical research, in new uses of improved and developing technologies, and in prevention, education, and control programs. Basic research continues to provide new understandings of disease and disease processes.

Atherosclerotic obstruction of arteries is a major cause of heart attacks, strokes, and occlusive disease of the peripheral vessels. New understandings of the basic biological processes that produce hardening of the arteries have contributed to improvements in the treatment of a number of circulatory diseases. Familial hypercholesterolemia is a rare genetic disorder that causes afflicted persons to have up to 8 times the normal level of blood cholesterol. Individuals with the disorder develop heart disease early in life and generally die of the disease in their early 20's. The Nobel Prize winning work of two NHLBI-supported researchers has determined the cause of the disorder to be either an absence or a defect of receptors for low density lipoprotein (LDL) cholesterol on cellular surfaces. This fundamental insight has led to the development of a new therapeutic approach to lower elevated blood cholesterol levels in patients with the most severe form of familial hypercholesterolemia. The liver takes up and degrades more cholesterol than any other organ because of its large size and its high concentration of LDL receptors. Therefore, replacing the liver in patients with the most severe form of familial hypercholesterolemia offers a direct way to increase substantially their supply of effective LDL receptors. This approach has been successfully applied in a 6-year-old girl who had already had several heart attacks and whose heart was so damaged that she received a heart transplant concurrently with the liver transplant. Over 6 months after the operation, the patient had a steady circulating cholesterol reading in the high normal range (300 milligrams per deciliter), which was approximately one-fourth her preoperative level (over 1200 milligrams). While liver transplantation is not expected to be a widely applied therapeutic approach to familial hypercholesterolemia, the success of the procedure indicates that enhancement of the number of functioning LDL receptors is an important research objective.

Hypertension, or high blood pressure, is considered a major risk factor for the most commonly encountered forms of heart and blood vessel disease. It is the most important contributing factor to the development of stroke, and it accelerates atherosclerosis in the coronary and peripheral blood vessels. Blood pressure regulation is a complex phenomenon involving interactions among a number of control systems, each of which includes the blood presssure sensing apparatus, blood pressure regulatory organs, and the blood vessels themselves. Biochemical modulators mediate feedback among the sensing apparatus, the regulatory organs, and the blood vessels.

Research is now focused upon one such recently identified modulator, atrial natriuretic factor (ANF), which is produced in the heart atria. ANF has been shown to increase the levels of sodium in the urine while also reducing blood pressure. Since its discovery in 1981, the extensive research on ANF has produced substantial advances in our understanding of its effects. The cloning and sequencing of the gene responsible for ANF synthesis has facilitated studies concerning the effects of ANF on the kidneys, the smooth muscles, and the renin-angiotensin system (a kidney-directed blood pressure regulating system). In addition to its demonstrated effects on kidney function, urine flow rate, and sodium and potassium excretion, ANF has also been shown to be a potent relaxant of large systemic arteries and other smooth muscles and to modulate the reninangiotensin system. The fall in blood pressure associated with the secretion of ANF is likely to be attributable to a combination of these observed effects. ANF appears to offer an exciting new avenue for the development of techniques to treat and possibly prevent hypertension, but further research must first be conducted to determine the role of ANF in regulating sodium balance, blood volume, and blood pressure homeostasis.

Results of community and population studies in the 1970's confirmed a familial pattern in hypertension. It is suspected that the disease has a genetic base and begins during childhood, but does not become manifest until adulthood. Other studies have shown that the rank order of juvenile blood pressure levels tends to be maintained over time for a few years and is related to changes in children's size and weight. Correlates of juvenile hypertension itself include increased heart rate and output, certain behavioral traits, and differences in sodium and potassium handling. Studies of adult essential hypertension suggest that there are several blood pressure control systems that contribute to blood pressure at any given moment and that influence each other's functioning, but little research in this area has focused on children. Because of this deficit in fundamental knowledge about pediatric hypertension, there is a lack of reliable indicators of the prehypertensive state and of knowledge of how to treat hypertension in children and adolescents. Multidisciplinary studies of pediatric hypertension are now needed, and efforts should be made, in human and animal studies, to identify variables in childhood that may be predictive of adult human hypertension.

Studies have been made of the interaction of stress and hypertension. Although psychological stress may contribute to high blood pressure, not everyone who experiences stress develops the problem. Animal research has shown that stress causes salt retention in young rats with a genetic tendency to develop high blood pressure. Normally, a temporary rise in blood pressure is corrected by an increase in the output of salt and water in the urine. Retention of salt would tend to prolong the rise in blood pressure. Salt retention may also affect blood vessel walls by increasing their reactivity to stimuli that result in an increase in blood pressure. Thus, retention of salt and water may be a mechanism by which stress leads to high blood pressure in persons with an inherited predisposition for the condition.

Technological advances in lasers and fiberoptics have substantially expanded opportunities for major advances across the continuum of research, from the understanding of basic processes to clinical applications in the treatment of a variety of cardiovascular disease manifestations. Although relatively few studies of laser effects on and interaction with cardiovascular tissues have been performed, and information about structural, physiological, and chemical effects of lasers are in an early stage of development, promising new therapeutic applications of lasers are already being considered for treatment of several cardiovascular conditions. To maximize therapeutic use of lasers and at the same time minimize untoward effects, the Institute considers it essential to initiate multidisciplinary research programs to investigate the fundamental effects of lasers and to promote coordinated research toward appropriate clinical applications.

Studies elucidating the function of the central nervous system in cardiovascular homeostasis have benefited from the application of techniques developed by neuroscientists. Hypertension research over the past decade has demonstrated, for instance, that the central nervous system is critical in maintaining elevated blood pressure. Many of the drugs effective in lowering high blood pressure work through centers in the brain. In addition, the brain has been shown to integrate circulatory responses, and it responds to chemical stimuli from other organs. Although major areas within the brain have been identified as control centers for cardiovascular regulation, there are probably several others that influence it. Further research is needed for identifying them as well as the pathways emanating from them.

One percent of all newborns have evidence of congenital defects. Although sophisticated surgical procedures have increased the lifespan and the quality of life of many of these persons, surgery is not always curative. In some cases, it is no more than minimally palliative. Pathologic studies have shown that 3 to 5 percent of all stillbirths have congenital abnormalities and that in 15 to 25 percent of spontaneous miscarriages, there is evidence of cardiac malformation. Basic information about the mechanisms that underlie normal development and about correlations of the various factors that direct normal development should lead to a firm foundation for understanding the etiology and pathogenesis of congenital heart malformations. It is now opportune to support interdisciplinary basic research on the fundamental processes of cardiac morphogenesis. The research, which would be with animal models, should be multidisciplinary and should link biochemical and structural observations with cellular, tissue, and organ function.

It is widely accepted that nutrition is an important factor in health and disease, and research has shown that certain dietary substances have specific effects on blood pressure. The consumption of excess dietary sodium, for instance, is believed to be a critical feature of essential hypertension in individuals who are referred to as "salt-sensitive." Very low sodium diets are helpful in lowering the blood pressure in hypertensives; primitive societies on lifelong low sodium intake do not show elevated blood pressures at older ages; and a number of animal species develop hypertension when fed high sodium diets. Similarly, diets higher in potassium tend to be associated with lower blood pressures. Evidence also suggests an association, in humans, of low calcium intake and high blood pressure, and a hypotensive effect of calcium loading; and limited experimental and clinical data suggest that magnesium concentrations are variable in hypertensive patients and that they too may variably influence the level of blood pressure. The biological mechanism or mechanisms by which nutrients influence blood pressure should be elucidated. An understanding of the basic mechanisms of blood pressure regulation and hypertension through the influence of nutrient substances will provide new information for the development of nonpharmacologic treatment of hypertension.

Population studies supported by the Institute have identified a number of risk factors that predispose to the development of cardiovascular disease. One of the risk factors for which there continues to be conflicting evidence is personality type. New evidence has now lent additional support to the theory that type A personalities who are by nature intense, time-obsessed, and prone to perceive many situations as stressful or challenging are more likely to develop severe cardiovascular disease than type B personalities, who do not display these characteristics. Extensive analysis of data from over 2,000 patients at Duke University who underwent coronary angiography and also completed a structured interview supports the existence of a relationship between type A behavior and coronary artery disease severity among patients below the age of 50. The hostility component of type A behavior was found to be even more closely related to disease severity than general type A behavior. This evidence of an interaction between age and type A behavior suggests that some earlier studies may have failed to show a clear link between type A behavior and coronary artery disease among younger patients because they did not consider age groups separately. Other research studies supported by the Institute are continuing to explore the role of personality in the development of coronary heart disease.

The effectiveness of population-based research studies such as the Framingham study in identifying and assessing the role of selected risk factors in the development of heart and vascular disease is often dependent upon the availability of inexpensive, accurate, and reproducible measurement methods. This is a particular problem in assessing the effects of physical activity and fitness on cardiovascular risk factors and end points. The presently available measurement tools are not sufficiently reproducible and valid to give consistently interpretable results. Because a number of present and planned studies supported by the Institute require accurate and reproducible measures of physical activity and fitness, research studies will be encouraged that will (1) validate and determine the reproducibility of currently available physical fitness questionnaires, (2) develop movement sensors and/or other devices that will allow objective measurement of physical activity, (3) validate a fitness test for use in field studies, (4) develop blood and other biological markers of current physical activity and fitness status, (5) analyze available longitudinal data to validate instruments for their ability to predict coronary events, and (6) develop new and insightful methodological approaches to the assessment problem.

Better treatment of coronary thrombosis has been suggested by recent research. It is now believed that many cases of acute myocardial infarction result from a blood clot occluding a coronary artery that supplies a segment of heart muscle. A promising but as yet unproven therapeutic approach to coronary care focuses upon agents to dissolve the clots in coronary arteries. It is believed that if the agents are administered shortly after the infarction occurs, the restored circulation to the affected areas of the heart muscle will limit the amount of heart muscle damaged. Since tissue death is likely to be complete within 6 hours of a coronary event, dissolution of a clot must be achieved rapidly for thrombolytic therapy to have a chance to reduce infarct size and thereby lower mortality due to myocardial infarction. With the knowledge that intracoronary administration of one thrombolytic agent, streptokinase, has been shown to be effective in recanalizing occluded arteries, the NHLBI established a study group in 1983 to assess the efficacy of intravenous administration of streptokinase and other thrombolytic agents in treating acute myocardial infarction. Intravenous administration is preferable to intracoronary administration because it can be done more quickly, it causes less discomfort to the patient, and it is less costly. Phase I of the trial was designed to assess the relative thrombolytic activity and side effects of intravenous tissue-type plasminogen activator and intravenous streptokinase in patients with acute myocardial infarction. The results of Phase I suggest that intravenous adminstration of tissue-type plasminogen activator represents a major therapeutic advance in thrombolysis. It produced recanalization rates comparable to intracoronary streptokinase (and almost twice the rate of intravenous streptokinase) without the inconvenience, risk, cost, or delay associated with intracoronary administration. The results of Phase I are being used in designing Phase II of the trial, which will directly address the question of the efficacy of recanalization in reducing tissue damage and mortality associated with myocardial infarctions.

Each year in the United States over 400,000 people die suddenly of coronary heart disease, a majority of whom had known coronary heart disease. Among those with known coronary heart disease, the largest sub-group consists of those individuals who have experienced a myocardial infarction (MI). In the first year following an infarction, an estimated 8 to 15 percent of the victims experience cardiac death. It is known that individuals with ventricular arrhythmias are at particularly high risk for sudden death. While a number of studies have attempted to evaluate the ability of antiarrhythmic drug therapy to reduce mortality in patients following an infarction, none has shown a significant treatment benefit, and in many there has even been a failure to show a positive trend. Unfortunately, in each of the previous studies there was some methodological problem. In order to resolve the issue, the Institute will initiate a clinical trial to test whether pharmacological treatment of asymptomatic ventricular arrhythmias occurring after a myocardial infarction can reduce the risk of sudden cardiac death and total mortality. A pilot study, the Cardiac Arrhythmia Pilot Study (CAPS), has demonstrated that patient recruitment is feasible and that good compliance can be achieved. The CAPS Policy and Data Monitoring Board recommended in September 1984 that planning should begin for a full-scale trial. The full-scale trial will be modeled after the CAPS in that post-MI patients with a clearly defined ventricular arrhythmia will be randomized either to active treatment or to a placebo. The trial result should provide important guidance to effective management for a large class of patients following an MI.

In May 1985, the Institute's Working Group on Mechanical Circulatory Support recommended to the NHLB Advisory Council that the goal of a fully implantable, long term, total artificial heart be actively pursued. The Working Group agreed that effective, fully implantable, long-term artificial hearts could provide a significant increase in lifespan for patients below age 70, with an acceptable quality of life for 17,000 to 35,000 persons annually. They estimated that the costs per person for a device, its implantation, and its maintenance for a projected average of 4.5 years of survival would be approximately $150,000. Such a mechanical circulatory support system would cost about the same as aggressive treatment of neoplasms, burns, and other serious disorders. Research should now be supported that would lead to the development of miniature tether-free electrically and thermally actuated implantable cardiac replacement systems. Such systems would include biventricular support, which assists the right and left ventricles remaining in situ, and the total artificial heart, which replaces the excised natural heart.

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987
Research Project Grants				
Number	1,709	1,709	1,665	1,648
Amount	360,291,000	345,064,000	337,610,000	338,920,000
Research Centers				
Number	22	22	22	22
Amount	42,535,000	40,737,000	40,737,000	38,058,000
Other Research				
Number	246	246	246	236
Amount	21,790,000	20,869,000	20,869,000	19,770,000

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987
Research Training				
FTTPs	1,145	1,089	1,089	1,015
Amount	25,350,000	24,279,000	24,279,000	21,343,000
Research and Development Contracts				
Number	155	155	155	150
Amount	43,770,000	41.574,000	41,574,000	40,404,000
Total				
Amount	493,736,000	472,523,000	465,069,000	458,495,000

National Heart, Lung, and Blood Institute

Lung Diseases

1987 Authorization: Indefinite.

Obligational Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$136,727,000	$130,852,000	$128,788,000	$126,984,000	$ -1,804,000

Purpose and Method of Operation

Respiratory diseases are among the leading causes of death and disability in the United States. About one in every five persons in this country reports some chronic respiratory problem, and chronic obstructive lung diseases are the fastest rising among the leading causes of death. When mortality from chronic obstructive pulmonary disease (COPD) is combined with bronchitis, bronchiectasis, and emphysema, these conditions accounted for 53,159 deaths in 1980. Provisional figures for 1984 indicate that COPD and allied conditions including asthma caused 69,760 deaths, or about 3.5 percent of all deaths in the United States. COPD and allied conditions now rank fifth among the 10 leading causes of death in the United States. Of increasing concern is the 25-percent increase for COPD between 1970 and 1982. This increase includes more than a doubling of the death rate for white females and a 67-percent increase for nonwhite females. Previously, rates were very low among women. Lung cancer death rates in recent years show similar trends; there has been a much greater increase for women than for men. Increased cigarette smoking among women appears to be a cause for the rising mortality from both lung cancer and COPD. In contrast, death rates for influenza/pneumonia, pulmonary embolism, and disorders associated with infant respiratory distress syndrome have declined rapidly over the same period. As the underlying cause, more than 250,000 deaths are attributed to lung diseases each year, and these diseases are a contributing cause to perhaps that many additional deaths. Thus, lung diseases cause one of every eight deaths and have a role in one of every four deaths.

Respiratory diseases are also recognized as an important cause of ill health and disability affecting large numbers of people. Chronic obstructive pulmonary disease and asthma are especially prevalent, afflicting nearly 8 million individuals in each case; over 15 million Americans altogether. Furthermore, a high proportion of asthma patients are young--almost 70 percent are below the age of 45--and in 1980 accounted for approximately 108 million days of restricted activity, 37 million bed days, and 9 million work-loss days. Asthma was also responsible for about 5.5 million visits to physicians' offices and 2.4 million days of hospital care. Chronic bronchitis affects an estimated 7.9 million persons of all ages, the majority of whom are in the workforce. Due to chronic bronchitis, there were in 1980 about 4.5 million work-loss days, 1.1 million hospital days, and 603,000 visits to physicians' offices. Many other respiratory problems, including disorders of pulmonary circulation, interstitial lung disease, pneumoconiosis, and neonatal pulmonary disorders, add to the overall picture of 24 million visits to physicians' offices and 20 million days of hospital care each year due to lung disease.

In 1982 lung diseases cost the nation's economy an estimated $26.4 billion in direct health expenditures ($7.6 billion), together with indirect costs of morbidity ($12.6 billion) and mortality ($6.2 billion). Direct costs measure expenditures on lung diseases for hospital care, physicians' services, and drugs. Indirect morbidity costs reflect lost productivity, measured in wages lost due to illness. Indirect mortality costs reflect lost potential productivity, measured in lost future wages by those who died of lung diseases prematurely (before normal life expectancy) in 1982. Thus, pulmonary diseases have cost our Nation greatly both in human suffering and in dollars. Although many of these diseases, once they occur, are chronic and incurable, many are preventable. Improved prevention and management of chronic pulmonary diseases provide a difficult and exciting challenge.

In the face of these data, the broad mission of the Lung Diseases Program is to provide more effective diagnosis, treatment, and prevention of pulmonary diseases. A multifaceted approach is taken through improved understanding of the causes of disease, greater knowledge of pathogenesis, and improved techniques for early diagnosis and more effective management. To these ends, seven program areas are emphasized, each representing a National Plan category: structure and function of the lung (including lung development); chronic obstructive pulmonary diseases (emphysema, chronic bronchitis, and asthma); pediatric pulmonary diseases (neonatal respiratory distress syndrome, bronchopulmonary dysplasia, cystic fibrosis, and bronchiolitis); occupational and immunologic lung diseases; pulmonary vascular diseases (pulmonary hypertension and thromboembolism, and edema); respiratory failure; and prevention, control, and education.

The Lung Diseases Program uses several mechanisms to support investigator initiated and Institute solicited research. Approximately three-fifths of the program's budget supports research project grants; 15 percent supports research centers; 15 percent supports career development programs, training and other grant research; and 10 percent supports research contracts. Research project grants include the traditional individual investigator-initiated research project, which are the major source of fundamental research contributing to our understanding of normal lung function and the processes involved in respiratory disorders, and leading to improvements in the diagnosis and management of pulmonary diseases. From time to time, the Lung Diseases Program augments its research portfolio by publishing a request for applications in a specific area of science. These special solicitations are designed to encourage exploration of problems not being addressed or being insufficiently addressed by investigator initiated grants. Areas are selected for emphasis through working groups, workshops, and task forces as well as by the Pulmonary Diseases Advisory Committee and the Lung Program's professional staff. The Lung Diseases Program also supports the Small Business Innovation Research Awards to establish the technical merit and feasibility of research and development ideas that may lead to a commercial product or service.

Center grants support a spectrum of activities with a multidisciplinary focus on a specific disease, entity or biomedical problem; they are developed in response to an announcement to fulfill a specific programmatic need. The Lung Diseases Program currently supports specialized centers of research in chronic diseases of the airways, respiratory diseases of neonates and children, occupational and immunologic pulmonary diseases, pulmonary vascular diseases, and adult respiratory failure. The expansion of these programs through a demonstration and education component for testing the effectiveness of interventions to promote health or prevent disease in defined populations is planned.

To meet the needs for research training and career development in the pulmonary field, the program supports a variety of career development, and individual and institutional training awards. The National Research Service Award (NRSA) include individuals at the predoctoral and post doctoral level, senior fellows who wish to acquire new research capabilities, and medical students who wish to acquire research training during off-quarter or summer periods. The recently initiated NRSA Minority Summer Program for Pulmonary Research encourages qualified minority school faculty members and graduate students to develop interests and research skill. In the career development area, the Clinical Investigator Award, the Physician Scientist Awards and the Research Career Development Awards are the main mechanisms of support.

Research and development contracts are another mechanism available to develop and apply new knowledge or to test, screen, or evaluate a product, material, or device, for use by the scientific community. Contracts are often the mechanism of choice for large-scale clinical trials or other clinical studies, where the parameters and methodology are specified with considerable detail.

Rationale for the Budget Request

The 1987 budget request for the Lung Diseases Program is $126,984,000, a decrease of $1,804,000 from the 1986 level of $128,788,000. This budget request permits progress toward long-term goals in a way that is consistent with the overall budget strategy of reducing the Federal deficit, and will enable the Institute to build on the current state of knowledge of lung diseases and to take advantage of the important scientific opportunities.

Despite several decades of investigation, factors other than cigarette smoking that define individual susceptibility to chronic obstructive pulmonary disease remain largely undefined. Although multiple occurrences of chronic obstructive pulmonary disease in certain families and the familial aggregation of level of lung function have been reported, the specific genetic and environmental contributions that underlie these observations remain obscure. Path analysis is a statistical technique that is used to identify patterns of hereditary and environmental sources of familial inheritance for traits such as lung function. It has recently been applied to a study of the relative contributions of heredity and environment to individual susceptibility to chronic obstructive pulmonary disease. Interestingly, there was evidence of a significant genetic effect on the pulmonary function measures in the study population: between 40 and 50 percent of the variability in the measures of pulmonary function could be explained by underlying genetic differences among individuals. These data suggest that there is an important genetic component in individual levels of pulmonary function, and further studies are necessary to confirm and extend these important findings.

Epidemiologic and anecdotal data and animal studies point to an association between smoking and the development of chronic obstructive pulmonary disease. Not all smokers develop lung disease, however, and this intriguing phenomenon has led to the postulation that some endogenous or perhaps even exogenous risk factors superimpose on the effects of tobacco smoke to produce the disease. It now appears that carriers of the gene for cystic fibrosis (CF), who constitute 4-5 percent of all white Americans, may be at risk of developing pulmonary disease if they smoke. Recent studies have shown that patients with CF or asthma, and parents of CF patients, exhibit abnormalities in their neural control mechanisms for secretory activities of their exocrine glands (increased cholinergic and decreased beta-adrenergic responses). Several studies indicate that these abnormal autonomic responses predispose to airway reactivity which may contribute to the development and progression of obstructive pulmonary disease, although additional genetic and environmental influences may also be involved in development of the disease. Parents of CF patients who are symptomatic seem to show smoking and age related accelerated decline in pulmonary function. Pulmonary function of CF parents seems to decline about twice as rapidly as controls if they smoked and somewhat less rapidly if they did not smoke. This was especially true in fathers. Thus, CF heterozygotes may be at risk for developing pulmonary disease, especially if they smoke, and confirmation of these findings will provide an important basis for smoking cessation in this group.

The biochemical defect in CF is not known, and methods for prenatal detection of the disease or for identifying the asymptomatic carriers of the CF gene are not available. Recombinant DNA techniques, which proved successful in identifying the genetic markers in other diseases such as Huntington's Disease, are now being used to attempt to locate the CF gene. This approach has been greatly facilitated by the recent fortuitous availability of tissues, blood components, and clinical histories from a unique population group with a high incidence of what might be a clinically and genetically homogeneous disease. Blood samples have been collected from members of this pedigree and appropriate cell lines have been established. Sufficient DNA has already been prepared from selected cell lines. The genomic DNA will be digested with appropriate enzymes, and the size and nature of the DNA fragments specific for CF will be characterized employing recombinant DNA techniques. The discovery of the map location of the CF gene by linkage to a DNA marker should permit the development of a prenatal test for CF. Eventual extension of these studies to the cloning and characterization of the CF gene, if accomplished, may lead to a test that is capable of detecting carriers of the CF gene.

Analysis of data from the Intermittent Positive Pressure Breathing study and from the Johns Hopkins Lung Project show that airways obstruction appears to be a major risk factor for the development of lung cancer. Male smokers with chronic airways obstruction were shown to be at significantly greater risk for developing lung cancer than their non-obstructed counterparts. Moreover, an increase in the degree of airways obstruction correlated with an increase in risk of development of lung cancer. These data suggest that smokers who will eventually develop lung cancer may be recognized by their prior development of ventilatory obstruction. This information should help health care workers to focus early detection efforts for lung cancer on an identifiable high risk group. Also, knowledge of the association might be a powerful motivating factor for individuals with airways obstruction to stop smoking. This striking clinical association should lead to new efforts to seek and examine factors common to the development of these disease processes.

An inner-city educational program to teach children with asthma and their families how to manage the condition has shown that health care costs can be significantly decreased in a group of children with a history of asthma problems. The program was conducted in four inner-city hospitals in New York City with asthmatic children and their parents. Participants learned what to do in case of an asthma attack, how to make decisions about activities that might cause an attack, how to communicate with doctors and others, and how to solve problems related to asthma. Results showed that for children who had been hospitalized once in the year prior to the program, emergency room use was cut in half, while it remained constant for the control children. Hospitalizations also decreased substantially for the experimental group as compared to controls. The resulting savings in health care costs for this group of children were $14.58 saved for every $1.00 spent on health education. These findings indicate that many hospitalizations and emergency room visits could be prevented if children and parents were educated for self-management of asthma and took more responsibility for keeping themselves healthy.

Current investigations are providing the basis for developing new therapies for several pulmonary diseases. As reported last year, the Institute has initiated the planning phase of a clinical trial to evaluate whether high frequency ventilation is superior to standard mechanical ventilation in providing ventilatory support to premature infants. Roughly 1,000 infants will be enrolled at ten hospitals. The results of the trial will show whether high frequency ventilation can reduce significantly both the incidence of chronic lung diseases in premature infants and the period over which mechanical ventilation must be employed. Whatever the results, the outcome of this study should have profound effects on the methods used to ventilate premature infants.

Pulmonary embolism is a major health problem with significant morbidity and mortality. An accurate diagnosis is essential as it has been estimated that mortality in correctly diagnosed and treated patients is approximately 8 percent, but mortality in undiagnosed and untreated patients is as high as 30 percent. The currently used methods for diagnosing pulmonary embolism are ventilation-perfusion scanning and angiography; however, they have several disadvantages, including lack of sensitivity, specificity, or they are invasive. A new imaging technique is being developed for diagnosing pulmonary embolism that would overcome these disadvantages. Monoclonal antibodies specific for the terminal region of human fibrin have now been isolated. The monoclonal antibody is highly specific for an antigenic site on the fibrin polymer of the clot and does not react with fibrinogen. Specific antibody is labelled with a radioactive tracer and injected into animal models with experimental femoral vein thrombosis. The venous thrombi accumulate large amounts of the labelled antibody, making it possible to image the clots from 4 to 48 hours after injecting the antibody. The fibrin antigenic site to which the antibody has been raised is identical in dogs and humans. This same technique can be used to image pulmonary thromboemboli. Its development for use in humans will be the next important step to take.

In the alveoli of the lung the surface tension at the air-liquid interface is lowered by the presence of a lipoprotein complex called pulmonary surfactant. The importance of pulmonary surfactant becomes evident in prematurely born infants deficient in this lipoprotein complex who manifest respiratory distress syndrome (RDS). Understanding the functional significance of surfactant proteins is of increasing interest because of the possibility of using artificial and animal derived surfactant for treatment of diseases associated with surfactant deficiency, in particular, neonatal RDS. Many of the exogenous surfactant preparations now under study contain small amounts of protein. As yet, virtually no information exists on the potential immunologic consequences of intratracheal administration of microgram amounts of foreign protein into sick, immature infants. If surfactant proteins are essential for surfactant function, it is very likely that human proteins produced by molecular biology techniques and subsequently purified would be the preferred co-ingredient with surfactant lipids for use in replacement therapy. Institute-supported investigators working in collaboration with California Biotechnology, Inc. have recently determined the entire sequence of amino acids in canine and human surfactant apoproteins of molecular weight 28-36 kilodaltons. Researchers working at the same firm announced earlier this year that they have cloned the gene for the protein component of the human surfactant. By implanting the cloned gene in cultured human cells, the scientists can now synthesize large quantities of surfactant protein. These recent findings will provide the molecular probes for future studies to determine the structure and regulation of the gene or genes responsible for encoding of surfactant protein. They also make it possible for investigators to study gene expression (i.e., its role and function) during lung development, and to generate human surfactant associated protein for possible clinical use. As discussed above, the availability of a human surfactant preparation would probably be the best choice for use with lipids as surfactant therapy for neonatal RDS. This new work will also help medical researchers understand just how the surfactant protein works. If abnormalities of the surfactant gene are important in neonatal RDS, they could potentially be used for prenatal screening for infants at risk of developing the disease. Thus, both basic and clinical research related to surfactant can be expected to benefit as a result of the extension of these recent findings.

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987
Research Project Grants				
Number	527	527	514	508
Amount	91,404,000	87,480,000	85,416,000	85,310,000
Research Centers				
Number	21	21	21	21
Amount	21,683,000	20,791,000	20,791,000	17,820,000
Other Research				
Number	117	117	117	122
Amount	8,457,000	8,095,000	8,095,000	8,433,000
Research Training				
FTTPs	339	324	324	300
Amount	8,873,000	8,492,000	8,492,000	7,767,000
Research and Development Contracts				
Number	22	22	22	25
Amount	6,310,000	5,994,000	5,994,000	7,654,000
Total				
Amount	136,727,000	130,852,000	128,788,000	126,984,000

National Heart, Lung, and Blood Institute

Blood Diseases and Resources

1987 Authorization: Indefinite.

Obligational Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$118,026,000	$112,957,000	$111,006,000	$108,569,000	$ -2,437,000

Purpose and Method of Operation

For decades, the illnesses, deaths, and health care costs resulting from blood disorders were incompletely reported, and the quantities and costs of blood collected, processed, and transfused were not reported at all. Recent findings have revealed the widespread involvement of blood disorders in death and disability -- for example, the role of thrombosis in the pathology of many disorders.

Blood diseases are chronic disorders. The genetic blood diseases such as hemophilia, sickle cell anemia, Cooley's anemia, and G-6-PD deficiency have lifelong effects on several million Americans. In the aggregate, they are the primary cause of death in as many as a thousand patients per year. Their chronic effects, however, range from mild to life-threatening and from transitory to continuous, and they result in major morbidity and cost for the health care system.

The acquired diseases in which abnormalities of the blood are prominent, such as coronary and cerebral thrombosis, phlebitis, and other thromboembolic conditions, affect additional millions of Americans. In 1982, blood diseases were reported as the primary underlying cause of 329,000 deaths in the United States. More recently, in 1983, blood diseases were the primary reason for 6.7 million patient visits to physicians' offices and 17.5 million days of hospital care. In 1982, the estimated economic costs (expenditures for hospital care, professional services, nursing home care, drugs, and medical sundries, productivity lost through illness or death) amounted to $29.9 billion.

There are almost two dozen blood products transfused to patients, and they range from whole blood to individual proteins separated from plasma. In 1980, 10.8 million units of whole blood were collected in the United States, and 37 thousand units of white cells and 564 thousand units of platelets were collected by apheresis procedures. While the collection of whole blood increased by 24 percent during the 1970's, the contribution by paid donors diminished to as little as 2 percent of the total. Over this same period, there was a trend away from the transfusion of whole blood (5 million units in 1971; 2 million in 1980) in favor of component therapy. The use of red cells, platelets, plasma, and cryoprecipitate increased by 400 percent over the period 1971-1980.

Adverse effects of transfusion remain, nevertheless. The recipients of whole blood, its components, derivatives, and substitutes occasionally experience transfusion reactions. The most frequent is hepatitis, the most severe is acquired immunodeficiency syndrome (AIDS), both of which are of major concern to the NHLBI.

The incidence of transfusion-transmitted hepatitis in multiple transfused patients who have received whole blood or red cells is at least 7 percent and possibly as high as 10 percent. Over 90 percent of these cases are caused by non-A, non-B hepatitis virus, the rest largely by infection with the B hepatitis virus. With approximatley 3.5 to 4.0 million individuals transfused with whole blood or red cells annually, the estimated incidence of transfusion-transmitted hepatitis in 1980 is 264,000.

In order to address these issues, the NHLBI Blood Diseases and Resources Program is organized into four major categories: thrombosis and hemostasis, which include thromboemolic, platelet, and hemorrhagic disorders; red blood cell disorders, which include the thalassemias and aplastic anemia; sickle cell disease, which includes sickle cell diseases and variants and sickle cell trait; and blood resources, which includes blood component and derivative therapy, safety of blood therapy, immunohematology, blood substitutes, and blood resource management. In these areas, the Institute's mission is the support of research designed to reduce the morbidity and mortality caused by blood diseases, to lead to the primary prevention of these diseases, and to ensure the availablity of adequate supplies of safe and effective blood products. The general principles in developing these programs include the encouragement of the scientific community to participate in the full range of investigative opportunities available in basic research, clinical research, clinical trials, applied and developmental research, and demonstration and education research, as well as to assist emerging disciplines and specialized areas of medicine to develop, upgrade, or organize their activities in ways that create a climate favorable for productive research and conducive to sophisticated investigations. The Institute is also committed to assure an adequate supply of investigators capable of competing successfully for research support by providing training and development opportunities that encourage potential candidates to consider research early in their careers.

The Blood Diseases Program uses several mechanisms to support investigator initiated and Institute solicited research. Approximately three-fifths of the program's budget supports research project grants; 20 percent supports research centers; 10 percent supports career development, training and other grant research; and 10 percent supports research contracts. Research project grants include the traditional individual research project, which are the major source of fundamental research contributing to our understanding and management of blood diseases and blood related disorders. As the need arises the Blood Program publishes a request for applications in a specific area of science. These special solicitations are designed to encourage exploration of problems not being addressed or being insufficiently addressed by investigator initiated grants. The areas selected for emphasis through working groups, workshops, and task forces as well as by the Blood Diseases Advisory Committee and the Blood Program's professional staff. The Blood Program also supports the Small Business Innovation Research Awards to establish the technical merit and feasibility of research and development ideas that may lead to a commercial product or service.

Career development awards such as the Transfusion Medicine Academic Award encourage medical schools to develop curricula in cooperation with blood centers which will foster the career development of aspiring scientists with outstanding potential as independent researchers or teacher-investigators. Other research awards seek to strengthen the training of minority individuals and institutions for biomedical research through the minority faculty development award and the minority biomedical research grant.

The Blood Program supports two kinds of centers: Specialized Centers of Research (SCORs) and Comprehensive Centers. The Specialized Centers of Research support a spectrum of multidisciplinary activities with a focus on a specific disease entity or biomedical problem. The Institute currently supports SCORs in thrombosis, which seek to improve the diagnosis, treatment, and prevention of thrombosis. In 1985, the Institute initiated a new SCOR program in transfusion medicine. These centers will expedite the development and application of new knowledge essential to ensure an adequate supply of safe and effective blood products. The Blood Program also supports the Comprehensive Sickle Cell Disease Centers. These centers continue to further our understanding of the impaired immune function and increased susceptibility to infections associated with sickle cell disease.

Research and development contracts are another mechanism available to develop and apply new knowledge or to test, screen, or evaluate a product, material, device, or component for use by the scientific community. Contracts are often the mechanism of choice for large-scale clinical trials or other clinical studies, where the parameters and methodology are specified with considerable detail.

Rationale for the Budget Request

The 1987 budget request for the Blood Diseases and Resources Program is $108,569,000, a decrease of $2,437,000 from the 1986 level of $111,006,000. This request permits progress toward long-term goals in a way that is consistent with the overall budget strategy of reducing the Federal Deficit. Indeed, there is considerable progress as shown by the following examples of the past accomplishments and future plans.

In the area of blood resources, recent scientific advances have changed transfusion practices, improved transfusion safety, provided efficiency in blood resource management, and extended the benefits of inpatient care. During the past decade, scientists have discovered properties of many previously unknown blood constituents and learned how to isolate them effectively. As a result, the benefits derived from blood donations have been greatly expanded through the use of components in increasingly specialized and effective forms of therapy. Progress has also resulted from the development of integrated facilities, where public participation in blood donation is organized, specialized equipment and personnel for testing and separating blood constituents are housed, and inventory management and distribution are centralized.

It is timely, therefore, that the NHLBI should support broad-based, multidisciplinary research in transfusion medicine that would expedite the development and application of new knowledge essential to ensuring an adequate supply of safe blood and blood products to effectively treat all in need. This research would address the technical and scientific problems associated with blood resources, and well-founded research in demonstration and education relative to blood resources would also be encouraged as part of this program. For these reasons the Institute started a Transfusion Medicine Specialized Center of Research Program and now supports 3 centers.

Research efforts will range from basic to applied in the development of new blood products and of methods to improve and assure the stability and safety of these products, and will also focus on expanding the knowledge of the consequences of transfusion. These activities may involve the biogenetics; coagulation biochemistry cell structure; virology; the technology of fail-safe, donor-patient identification; or the development of sophisticated, computerized systems for inventory management. Clinical studies of new or unproven therapies are a necessary part of this program, since blood collection entails long-term contact with many thousands of healthy individuals within the community. Such collection also provides a favorable opportunity for epidemiological investigations of blood-related problems, and also of problems in other fields, such as cancer and heart disease. Epidemiological studies of the relationship between blood transfusion and AIDS, for example, are readily implemented in this kind of setting.

Significant recent information about the molecular and cellular pathology of sickle cell disease has improved our understanding of phenomena such as hemoglobin S polymerization, erythrocyte membrane injury, and abnormal blood rheology. Nevertheless, the linkages of these recognized abnormalities to specific clinical events in sickle cell disease patients have not yet been clearly established. Important complications of sickle cell disease are still defined by descriptive terms such as "chest syndrome" or "painful crises." In large part, this situation has been brought about by the limitations of conventional diagnostic and imaging techniques. Few, if any, of the techniques currently employed can be used to identify groups at high risk for infarction or to demonstrate impeded flow in the small blood vessels.

Arteriography is not without significant risks, and in sickle cell disease it could theoretically make matters worse by transforming a partial obstruction into complete occlusion. Substantial improvement in medical imaging technologies, however, has occurred in the last few years, and noninvasive techniques provide opportunities to study the clinical manifestations of sickle cell disease. Positron emission tomography, magnetic resonance spectroscopy, Doppler ultrasound, and thermography offer new prospects for studying blood flow and metabolism in tissues and organs. Results of such studies could lead to the development of methods for following the status and progress of sickle cell disease, including the changes that are characteristic of the recurrent sickle cell "crisis." The NHLBI will seek to encourage the application of these new techniques by support of pilot projects for safer, more accurate diagnosis of the several clinical mainfestations of sickle cell disease. The new, noninvasive, computer assisted diagnostic technologies used with standard methods appear to be well suited to a systematic investigation of the mechanisms involved in the pathophysiology of these syndromes. These methods could also enable measurements that might be used as a guide to patient management. Research to assess the potential application of new technologies to sickle cell disease is necessary, for, although diagnostic imaging is widely supported at NIH for other diseases, no investigation of sickle cell disease are under way using this concept. The true usefulness of these approaches can be determined only when a large number of patients are followed over time. If pilot data appear promising, studies can be designed to ascertain their value either in the diagnosis or management of complications in sickle cell disease patients.

Patients with inherited deficiencies of protein C are at greater risk of thrombosis. Since the anticoagulant activity of protein C is dependent upon protein S, patients lacking functional protein S might also be expected to experience thrombotic disease. Because these newly found substances regulate coagulant and fibrinolytic activities, their clinical potential is enormous. These proteins have been shown to decrease in patients who have undergone major surgery. Deficiencies or functional defects in protein C and protein S can be corrected, at least in part, by replacement therapy. Thrombotic complications following major surgery may be prevented by beginning prophylactic treatment with protein C and protein S. Unlike other therapies, these new agents are selective, occur in localized areas, and are self-limiting. They offer the promise of a previously unachievable measure of control over the blood clotting and clot dissolution processes.

Patients with Cooley's anemia must undergo transfusions of red blood cells in order to treat severe anemia. The transfusions, however, cause a variety of problems such as the accumulation of toxic amounts of iron in the recipient, and exposure to transfusion transmitted diseases. In addition, because of repeated transfusions, most patients with Cooley's anemia become sensitized to white cells and platelets, which are present in fresh blood. For this reason, frozen red cells are routinely used because the freezing, thawing, and washing removes most of the white cells and platelets. However, because one-third of the red cells are lost in the process, more units of blood are required to provide the amount of red cells needed by the patient. Investigators are now preparing red cells from fresh blood, using a filter to remove white cells and platelets. More than 500 transfusions have been given using red cells prepared this way, and no adverse reactions have been reported. Recent results indicate that, when compared to using frozen cells, this method results in a 36-percent better yield of red cells, an increase in the oxygen-delivery capacity of the blood, and, therefore, a decrease in the overall number of transfusions required. The average Cooley's anemia patient now needs only two units of red cells per month at $48 per unit as compared to three units per month at $105 per unit when frozen blood is used. Investigators are optimistic that this new technique for preparing red cells might be used to transfuse all Cooley's anemia patients, since the cells are easier and therefore less expensive to prepare, are more effective, and have a greater yield. In addition, patients are subjected to fewer donors, thereby reducing the risk of contracting diseases transmitted by blood.

More than 50,000 Americans of African, Mediterranean, mid-Eastern, and Indian origin are affected by sickle cell disease. Medical costs for these individuals range from a few thousand to hundreds of thousands of dollars annually and constitute a major public health expenditure. Additional costs accrue as a result of time lost from school or employment and from the attendant psychosocial affect on the patient. No known drugs are available that safely and effectively prevent or alleviate sickle cell crises. One collaborative study is focused on development of a drug with a stereospecific inhibitor. This approach involves the rational design or selection of compounds that prevent gelation when bound at specific sites on the sickle hemoglobin molecule. The hemoglobin binding sites of two potent antisickling agents, ethacrynic acid and a structural analogue, have been determined with the use of X-ray crystallographic techniques. The study suggests a possible molecular mechanism of action for antisickling properties of these drugs. These studies provide important basic information about the environment of sites where compounds that bind to hemoglobin have potential clinical use as antisickling agents. Research in other areas indicates that sickle cell patients experience a significant change in the proportion of dense red cells during crises. A new method of density measurement, with potentially good results, has been used to monitor sickle cell crises. Called red cell distribution width (RDW), the method estimates red cell size calculated from Coulter counter determination. It provides a convenient alternative to the density gradient methods currently in use. The development of an effective antisickling agent and a reliable means of monitoring sickle cell crises will greatly enhance the treatment mechanisms available for sufferers of this disease and will reduce the severity of morbidity and the rate of mortality associated with it.

Several assays that have been developed to detect AIDS antibodies have recently been approved for commercialization. In addition, DHHS approval of regulations for HTLV-III testing is imminent. The enzyme-linked immunoabsorbent assays (ELISA) have demonstrated much greater determinant and predictive sensitivity than have previously available tests. Since June 1985, nearly all the nation's blood has been screened with these radioimmunoassay techniques. The true efficacy of the assays will be determined during the next 5 years. To date, there have been no reports of AIDS contracted through transfusion of blood since ELISA testing was implemented. Continued and expanded research is necessary to exploit fully the potential of radioimmunoassays to detect contaminated blood products from persons with the virus. In addition, studies are needed to develop assays for the virus itself, to develop methods to inactivate HTLV-III in blood and blood derivatives, and to assess the risk of contracting AIDS.

Hepatitis continues to be the disease most frequently transmitted by blood transfusions. As previously noted, non-A, non-B hepatitis now surpasses hepatitis B. Recipients of blood transfusions are much more likely to contract NANB or hepatitis B than AIDS. The causative agent(s) for non-A, non-B hepatitis has not yet been identified. Isolation of the NANB agent(s) could open the door for the development of specific assays of the agent(s) in the blood supply and for development of vaccines against the virus, and thus greatly reduce the morbidity and mortality related to this disease.

Cytomegalovirus (CMV) is another disease transmitted by blood. It is thought that all elements of human blood transmit CMV, and the disease has been associated with immunosuppression and is particularly severe for infants and transplant recipients. To date, there is no effective means of preventing or treating CMV infection, but research continues on methods to identify infectious units of blood.

These areas of research will continue to contribute to the safety and well being of the nation's health and will help accelerate sorely needed resolutions of the pressing issues in the area of blood diseases.

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987
Research Project Grants				
Number	468	468	456	449
Amount	81,257,000	77,519,000	75,568,000	74,676,000
Research Centers				
Number	17	17	17	17
Amount	22,317,000	21,286,000	21,286,000	19,879,000
Other Research				
Number	72	72	72	77
Amount	5,469,000	5,217,000	5,217,000	5,494,000

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987
Research Training				
FTTPs	226	214	214	185
Amount	5,983,000	5,706,000	5,706,000	4,659,000
Research and Development Contracts				
Number	12	12	12	14
Amount	3,000,000	3,229,000	3,229,000	3,861,000
Total				
Amount	118,026,000	112,957,000	111,006,000	108,569,000

National Heart, Lung, and Blood Institute

Construction

1987 Authorization: Indefinite.

Obligational Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$3,300,000	$3,158,000	$3,158,000	---	-$3,158,000

Purpose and Method of Operation

This program was initiated in FY 1985 to defray the cost of repairs, renovation, remodeling, or construction of physical facilities for organizations that have a core of research activities in at least two of the three major programmatic interests of the Institute and which need improvement facilities in order to utilize contemporary techniques and methods to expand and improve their research activities.

These research facilities serve several research projects on a shared basis. Examples are tissue and cell culture research laboratories, imaging facilities, and biocontainment facilities.

Rationale for the Budget Request

The 1987 budget request does not include funds for construction.

National Heart, Lung, and Blood Institute

Intramural Research

1987 Authorization: Indefinite.

Obligational Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$60,790,000	$58,150,000	$58,150,000 (FTEs: 412)	$56,065,000 (412)	-$2,085,000 (--)

Purpose and Method of Operation

The NHLBI Division of Intramural Research conducts both clinical and basic research relating to diseases of the heart, lung, and blood. Collaboration exists among the various laboratories and branches within the NHLBI and with scientists from the other NIH Institutes to enhance its overall research strategy. In addition, the scientific community in the United States and abroad benefits from the knowledge and participation of clinicians and researchers from other nations who contribute to the latest biomedical research developments.

The Division allocates its resources to further the knowledge and develop improved techniques and therapies for the cardiopulmonary, blood, and endocrine systems in health and disease. There are 18 laboratories or branches in the Division and the following brief descriptions provide an insight into the overall NHLBI intramural research programs.

The Laboratory of Biochemistry conducts basic research on enzymes, metabolic regulation, and protein chemistry. The interaction of these mechanisms provide a better understanding of the biochemical processes as they relate to the cellular systems.

The Laboratory of Biochemical Genetics conducts basic research in neurotransmission. Some of these studies seek to: determine the basic mechanisms that regulate the expression of genes during cell differentiation; identify the control mechanisms involved in the organization of neurotransmitter regulators and their role in the function and development of the nervous system; and explore the regulation of adenylate cyclase activity and its role in gene expression.

The research interests of the Cardiology Branch focus on elucidating the mechanisms responsible for the dynamic alterations in coronary vascular resistance; defining the pathophysiology and treatment of coronary artery disease, angina pectoris, and hypertrophic cardiomyopathy; evaluating and treating valvular heart disease; and exploring the etiologies and treatment of dilated cardiomyopathy.

A major area of research in the Laboratory of Cell Biology is to understand the molecular processes that underlie muscle contraction and regulation. This knowledge has important applications in the study of cardiac and vascular diseases.

Many biochemical agents, such as hormones and drugs, affect the mechanisms that regulate the physiological and pathological processes of the pulmonary and cardiovascular systems. Research in the Laboratory of Cellular Metabolism concentrates on the enzymes responsible for the synthesis of these agents and their influence on cellular function.

The Laboratory of Chemical Pharmacology directs its research emphasis toward studies of the mechanisms by which drugs and their metabolities exert their toxic effects. In addition, methods have been developed for discovering drugs and other foreign compounds that cause tissue lesions through the formation of chemically unstable metabolities.

The experimental interests in the Laboratory of Chemistry are concerned with isolating, elucidating, and studying the structures and properties of biologically important compounds, including the application of nuclear magnetic imaging on biologically important molecules.

Red cell disorders that produce significant morbidity and mortality include thalassemia, sickle cell anemia, aplastic anemia, and various syndromes of bone marrow failure. Basic research in the Clinical Hematology Branch involves the most advanced technologies and conceptual knowledge on elucidating the pathogenesis and devising treatment for these disorders.

Studies in the Laboratory of Experimental Atherosclerosis define the nature of accumulated cholesterol within atherosclerotic lesions. Also, the affect of platelets on the pathogenesis of atherosclerosis is studied.

The Hypertension-Endocrine Branch conducts basic and clinical research on many aspects of the causes and therapy of hypertension. These studies focus on the neurohumoral and vasoactive systems that control the circulation. Studies on experimental therapeutics include: the developmental measurement techniques to study the pathophysiology of hypertension; the relationship of intracellular calcium levels to hypertension; and the examination of hormonal responses to salt in normal and essential hypertension. Research on biochemical pharmacology is directed toward understanding the neurochemical systems as they relate to blood pressure control.

The Laboratory of Kidney and Electrolyte Metabolism conducts studies on water and solute transport in cells in general and in kidney cells in particular, and on the mechanisms, hormonal and other, that control this transport.

Research in the Laboratory of Molecular Cardiology seeks to determine the molecular mechanisms regulating the interaction of major contractile proteins present in smooth, skeletal, and cardiac muscle.

The Molecular Disease Branch is conducting research that relates to the molecular and structural properties of the human plasma apolipoproteins, the physiological role of apolipoproteins and lipoproteins in lipid transport, and the mechanisms involved in the regulation of cellular metabolism and transport. Knowledge of these interactions is fundamental to the understanding of lipid transport and metabolism in normal individuals as well as in patients with disorders of lipid metabolism and atherosclerosis.

The Laboratory of Molecular Hematology conducts research on the basic molecular mechanisms of gene expression and protein synthesis using hemoglobin as a model system. Techniques using retrovirology and recombinant DNA technology are being developed for treating human genetic defects.

The development of new or improved surgical procedures for treatment of patients with congenital and acquired heart disease is the primary mission of the Surgery Branch. Areas of research include: evaluation of methods to ameliorate or eliminate the degenerative processes of prosthetic heart valves, evaluation of laser-angioscopy in patients with coronary heart disease, and the surgical assessment and use of new ultrasonic technologies.

Investigations in the Pathology Branch relate directly to studies of coronary, valvular, and congenital heart disease in human beings. Specifically, the morphologic aspects of the effects of toxic substances on the heart and the cardiovascular lesions associated with stress are studied. Also, studies evaluate the use of lasers as therapy for recurrent ventricular arrhythmias.

The research of the Pulmonary Branch centers on diseases of the alveolar structures in the lung where gas exchange takes place between the air and blood. Three categories of common diseases are investigated including: disorders characterized by destruction of the alveolar walls such as emphysema; interstitial lung disorders characterized by progressive fibrosis of the lung parenchyma such as idiopathic pulmonary fibrosis and asbestosis; and interstitial lung disorders characterized by the accumulation of T-lymphocytes in the lower respiratory tract including sarcoidosis, berylliosis, and hypersensitivity pneumonitis. Studies include the evaluation of the pathogenesis of these diseases and development of strategies to modulate the processes.

Efforts in the Laboratory of Technical Development are directed toward the design and fabrication of blood access and circulatory assist devices, and the fabrication of pumps and gas exchange devices. The instrumentation and methods developed in this laboratory apply recent advances in technology and pathophysiology to assist the failing lungs and heart.

Rationale for the Budget Request

The 1987 budget request for the intramural research program is $56,065,000, a decrease of $2,085,000 from the 1986 level of $58,150,000. The following are brief descriptions of some activities and program highlights for the intramural research area of the Institute.

Research studies continue to evaluate the pathogenesis of both hereditary and acquired forms of emphysema in an attempt to suppress those processes that cause destruction of the lower respiratory tract. Alpha-1-Protease inhibitor (Al-Pi) is an effective neutralizing agent for the potent enzyme elastase, the excessive activity of which is believed to result in an inherited form of human emphysema. By use of bronchoalveolar lavage, in which lung fluids can be safely removed for examination and analysis, it has been shown that Al-Pi provides the major anti-elastase protection in the lower respiratory tract and that Al-Pi is deficient in inherited emphysema. One approach to the treatment of this usually fatal disorder has been to augment the Al-Pi protection of the lungs. This augmentation was first attempted by trying to get the liver to release more Al-Pi and thus elevate the levels found in the lung. The use of the drug danazol, while increasing Al-Pi levels in the plasma by 50 percent above the baseline level of deficient individuals, did not elevate the level sufficiently to afford protection of the lungs against excessive elastase activity. A more direct approach has been to augment Al-Pi in the plasma by the use of Al-Pi itself. The recent availability of sufficient quantities of purified Al-Pi from human plasma has provided for a study of the feasibility, safety, and efficacy of replacement therapy in a group of patients with inherited deficiency of Al-Pi. Although the study is not yet complete, it appears that all these objectives will be achieved. An allied study using nonhuman primates and Al-Pi produced from the human gene cloned in yeast or bacteria is now planned.

The development of an ideal cardiac valve substitute remains a major problem in the area of cardiac surgery. All types of prosthetic heart valves currently approved by the FDA work well in the short term for periods of up to three years. However, over longer periods, there are relentless complications due to clot formation, anticoagulation, material wear, fatigue, or calcification. In addition, there is as yet no adequate prosthesis for the replacement of the tricuspid valve. A further clinical problem is the high incidence of death following mitral valve replacement. New prototype devices currently under test hold promise for improvements in the areas mentioned. In particular, more than 500 mitral and tricuspid valve replacements using prostheses of biological origin have been tested in animal experiments during the past four years. A persistent problem with the bioprosthesis is that of calcification, which is severe at 20 weeks. Recent studies have shown the effectiveness of surfactants, solutions lacking calcium and phosphorus, and new buffers, in mitigating the calcification process.

Essential to the successful surgical treatment of heart diseases of all kinds is the capability of protecting the heart for long periods (up to 5 hours) without oxygen. The conventional use of whole-body cooling and of cardioplegic solutions which cause the heart to stop beating are not adequate in all cases. Several protective additives have recently been analyzed using isolated heart preparations with manifestations of heart disease. These additives, phentolamine, amiodarone, and prostaglandin PBx, have been studied at normal body temperature and in the hypothermic state (20-25°C) Significant improvements in recovery of function after oxygen deprivation has been shown with these additives, the greatest recovery having been achieved with doses of 10 mg, 0.25 mg, and 100 mg of phentolamine, amiodarone, and prostaglandin PBx, respectively. Studies in animal models have utilized a newly developed miniaturized dual pH and temperature transducer, which measures conditions inside the heart. The results indicate that if the interstitial pH is maintained above 7.0 during oxygen deprivation, regardless of the method used, recovery of function ranges from 80 to 90 percent of starting values. With these various maneuvers, solutions, and conditions, oxygen deprivation intervals can be increased from 17 to 92 minutes by a single injection of a cardioplegic solution under very cold conditions.

Clinical and epidemiological studies have established that elevated plasma levels of LDL, and reduced levels of HDL, are associated with an increased risk of the development of premature cardiovascular disease. Cholesterol is transported in the blood in complexes of lipids and proteins of which there are five seperate classes including chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). The proteins in these complexes, known as apolipoproteins, have been studied extensively and the genes for the major human plasma apolipoproteins have been cloned and the gene structure determined. Several structural defects in apolipoprotein A-1 have been identified which are associated with reduced levels of plasma HDL. Several inherited conditions in man, involving defective lipid metabolism (hyperlipoproteinemia and hypertriglyceridemia) have been shown to be characterized by deficiencies in specific apolipoproteins. The elucidation of the molecular defects in patients with such diseases will permit the development of more specific diagnostic procedures, and will allow eventually for more effective treatments, including, ultimately, gene therapy.

An important research development is the use of magnetic resonance imaging non-invasively to monitor the concentration, turnover, and/or transport of many important metabolites and ions. MRI is a form of spectroscopy based on the properties of nuclides that possess a net spin and associated magnetic moment. These nuclides resonate at characteristic frequencies that can be detected with appropriately positioned magnetic fields and receiving coils. Since biological tissues are almost transparent to these nuclear magnetic properties, these types of studies can be conducted non-invasively on intact cells, animals, or humans with no side effects. For this reason, MRI permits the investigation of biochemical processes within cells, organs, or whole animals without the necessity of extensive surgery or sampling of tissue for analysis. One of the major preparations employed has been the intact heart. An MRI catheter probe has been developed which monitors the normal concentrations of adenosine triphosphate and creatine phosphate and demonstrates the metabolic time courses of total and localized oxygen deprivation in the heart. The study demonstrates that the high energy phosphate contents of a healthy heart do not vary within a cardiac cycle or when the work output of the heart has been increased up to three-fold. The study also demonstrates that a diseased heart may show signs of high energy metabolite shifts much sooner than a healthy heart, thus potentially providing a sensitive diagnostic technique.

National Heart, Lung, and Blood Institute

Research Management and Support

1987 Authorization: Indefinite.

Obligational Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$36,099,000	$33,904,000	$33,904,000	$35,584,000	+$1,680,000
		(FTEs: 406)	(406)	(--)

Purpose and Method of Operations

This budget activity provides for the overall management of the Institute's research program as well as specific prevention, education, and control activities. It provides funds for the salaries and activities of the Office of the Director; the Division of Extramural Affairs; the Division of Heart and Vascular Diseases; the Division of Lung Diseases; the Division of Blood Diseases and Resources; and the Division of Epidemiology and Clinical Applications.

The last four divisions listed have responsibility for the management of research grant, research training, and research contract portfolios in their respective disease areas.

The Division of Extramural Affairs provides initial scientific merit review of program project and center grants and research contracts solicited by the Institute, facilitates the activities of the National Heart, Lung, and Blood Advisory Council, and assures the wise stewardship of Federal funds through proper grant and contract management.

The Office of the Director provides overall planning, direction, coordination, and evaluation of the Institute's programs. It is divided into five main staff offices -- the Office of Prevention, Education and Control, the Office of Program Planning and Evaluation, the Office of Administrative Management, the Office of Special Concerns, and the Office of International Activities.

The Office of Prevention, Education and Control develops and coordinates Institute policies and programs in the areas of information and education relating to heart and vascular, lung, and blood diseases. It conducts the Institute's National High Blood Pressure Education Program as well as other risk reduction activities related to cardiovascular and pulmonary diseases.

The Office of Program Planning and Evaluation advises the Director on program plans and policies. This office also performs analysis and evaluation of data on heart and vascular, lung, and blood diseases and on blood resources for use in program planning and development.

The Office of Administrative Management assists the Director on administrative matters, and directs administrative functions of the Institute including financial management, personnel management, material procurement, office services, and management analysis.

The Office of Special Concerns (OSC) serves as the focal point for all activities relating to the Institute's Equal Employment Opportunity (EEO), and special programs to increase minority participation in heart, lung, and blood research. The office advises the Institute on matters relating to compliance with the Civil Service, DHHS and other Federal equal employment opportunity policies and regulations. OSC also plans, coordinates, monitors, and evaluates the Institute's progress toward meeting objectives; and maintains liaisons with other NIH components concerned with EEO, minority and women's affairs.

The Office of International Affairs provides for the successful U.S. cardiovascular disease prevention and control programs and research which has acted as a catalyst to extend the opportunities for U.S. scientists to cooperate with colleagues throughout the world in projects of high national priority, mutual interest and benefit.

Rationale for the Budget Request

The 1987 budget request of $35,584,000 for research management and support is an increase of $1,680,000 over the 1986 level of $33,904,000.

This budget activity provides funds for the proper management and oversight of the Institute's programs. It also provides funds for specific program activities aimed at the prevention of heart, lung, and blood diseases in the United States. The National High Blood Pressure Education Program, for example, is an ongoing effort that has contributed significantly to the realization among our citizens that hypertension is a major health problem. In fact, the proportion of Americans with hypertension who are receiving treatment has steadily increased since 1972.

The success of the National High Blood Pressure Education Program has led the Institute to develop another major prevention program to make people aware of elevated blood cholesterol levels and the increased risk of heart disease associated with this condition. The Institute is currently implementing this new program, called the National Cholesterol Education Program (NCEP), with the help and advice of other Federal agencies, experts in this field, and various interested organizations. This budget reflects an increase of $238,000 for these programs.

Efforts to reach special audiences, such as minority groups, will be an integral part of outreach activities of the NCEP. Materials and programs responsive to the needs of these groups will be developed by the NCEP.

Several major medical associations have worked closely with the Institute on updated guidelines for treating and preventing heart, lung, and blood diseases. For example, the American Lung Association works jointly with the Institute in transferring into the community the research findings on preventing and controlling asthma. The American Heart Association is working with the Institute to develop small business worksite programs on heart and pulmonary disease risk factor reduction.

During 1987, the Office of Prevention, Education and Control will continue to support four major program priorities: reducing elevated cholesterol and on smoking cessation; promotion of the more systematic and timely transfer of education-related research; support of ongoing efforts in high blood pressure control, with emphasis on worksite programs and special populations, such as blacks and Hispanics; and continuation of information activities that provide services to the Institute as a whole.

Detail of Permanent Positions

	1985 Actual	1986 Estimate	1987 Estimate
ES-60	11	11	11
ES-61	8	8	8
Subtotal	19	19	19
GS/GM-15	32	32	32
GS/GM-14	71	71	71
GS/GM-13	61	61	61
GS-12	41	41	41
GS-11	56	56	56
GS-10	2	2	2
GS-09	59	59	59
GS-08	21	21	21
GS-07	94	94	94
GS-06	62	62	62
GS-05	49	49	49
GS-04	10	10	10
GS-03	4	4	4
GS-02	4	4	4
Subtotal	566	566	566
Grades Established by act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	2	2	2
Medical Director	35	35	35
Director Grade	16	16	16
Senior Grade	9	9	9
Subtotal	62	62	62
Ungraded	123	123	123
Total permanent positions	770	770	770

WEDNESDAY, MARCH 12, 1986.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

WITNESSES

DR. DAVID P. RALL, DIRECTOR, NIEHS
DR. THOMAS MALONE, DEPUTY DIRECTOR, NIH
CHARLES E. LEASURE, JR., EXECUTIVE OFFICER, NIEHS
ROBERT C. PATRICK, BUDGET OFFICER, NIEHS
DENNIS P. WILLIAMS, ACTING DEPUTY ASSISTANT DIRECTOR, BUDGET, DHHS

INTRODUCTION

Mr. NATCHER. At this time we take up the budget request for the fiscal year 1987 for the National Institute of Environmental Health Sciences.

And we have before the Committee Dr. David P. Rall, the Director. And, Dr. Rall, you have appeared before our Committee on many occasions. We are glad to have you back. And before you proceed with your statement, tell us who you have there at the table with you.

Dr. RALL. Thank you very much, Mr. Chairman.

As always, it is a pleasure indeed to be back again here before this Subcommittee.

I am sure you know, on my right, Dr. Tom Malone, who is the Deputy Director of NIH. On my immediate left, Mr. Charles Leasure, our Executive Officer. And farther left, Robert Patrick, our Budget Officer.

OPENING REMARKS

NIEHS is 20 years old this year, and we will have a celebration sometime in December. At our twentieth anniversary, even though it has been a very busy and lively 20 years, it is time to look back and spend a little time in the few minutes I will take this morning, describing what we have been doing in the last 20 years and mention a few of the specific accomplishments of the last year which are in the statement which I would like to submit.

STATUS OF ENVIRONMENTAL HEALTH SCIENCES

If you look back at environmental health sciences in 1966, the field was extremely young. It really was undefined. Rachel Carson had published her book. But the concept of a large research program in environmental health sciences simply had not yet begun.

In the 20 years, we have established a new scientific field, that of environmental health research. It is growing, it is lively, it has a long ways to go. But I think it is doing quite well.

Importantly, we have also built a cadre of scientists able to address those environmental health problems which we read about almost daily in the newspaper.

Now we have a science base. We know more about some of the most toxic agents than we knew 20 years ago. In fact, for many of them we really know enough to do a very intelligent job of regulation.

In the past 20 years, we have not only uncovered new health hazards of concern to everybody, but we also demonstrated that some chemical compounds are non-hazards. And that is important too. It does not make the headlines, but in terms of public health significance, it is critical. Most recently we identified the chronic toxicity and carcinogenicity of methylene chloride.

METHYLENE CHLORIDE

I want to spend a minute of on methylene chloride because the Wall Street Journal and other periodicals published articles saying methylene chloride is used to decaffeinate coffee, and suggest it is silly to be concerned since there is so little methylene chloride in decaffeinated coffee. The implication is that people need not worry at all about the human health effects of methylene chloride and with that, tend to dismiss the importance of the toxicity problems of methylene chloride. And I think that is misleading, because the major uses of methylene chloride are for paint removal. If you, as I used to do, have an old chest you wanted to clean up, you go down to the basement and use paint strippers and strip the paint off and then refinish it. The fumes in a closed room can easily exceed the amount that we expose the rats and mice to that cause cancer.

Twenty-five percent of methylene chloride is used in paint strippers, another 10 percent is used in a degreasing agents. If you wanted to clean your automobile and general other things, you would wash it in methylene chloride, and the opportunity for exposure is very great indeed.

And, finally, another 25 percent is used as a propellant in aerosol sprays. Even though I do not think anybody really thinks there is a very serious potential health problem from the few micrograms in decaffeinated coffee, the enormous amount of methylene chloride that you can be exposed to by paint removers, degreasers, and propellants is a matter of legitimate concern. And we are talking about a lot of compound. There is 500 million pounds of methylene chloride produced each year.

OTHER HAZARDOUS AND NON-HAZARDOUS SUBSTANCES

Other important discoveries were the toxicity of chlorinated paraffins, used as plasticizers, flame retardants, and such, compounds that we had thought were quite inert and would not be toxic. They are in fact potentially serious.

I have told you before the story of benzene and how this well-known human carcinogen has now been shown to be potent toxin for the bone marrow system, and at levels and concentrations that are present in the workplace.

Many years ago, our Institute was among the first to demonstrate the high toxicity of dioxin and its teratogenicity in very low doses. I am also sure you remember our many discussions about the toxicity of asbestos when inhaled.

But there are compounds we found to be non-hazards. This Committee, in fact, directed us to initiate a study in which asbestos, as it is found in drinking water, was shown to pose no hazard. I think that is of major importance. There were concerns some 10 years ago about the polychlorinated biphenyls in mother's milk, PCBs in mother's milk. We initiated a long-term prospective study and there seems to be no serious hazard to infants from PCB in mother's milk at the levels that are currently present.

THERAPEUTIC DRUGS

We have looked at three therapeutic drugs, medicines, recently, and they are all perfectly safe. These are compounds that were introduced before the 1962 Drug Amendments and were basically untested for long-term toxicity.

Among the other compounds we have shown to be non-hazardous are Vitamin C, which I have talked about before; ephedrin, which is extensively used as a nasal decongestant and was originally a plant product from China; and most recently an antihistamine, chlorpheneramine, which is in many of the cold tablets.

The kinds of testing done on these compounds are somewhat yes or no indications of toxicity. More recently we have begun to look at how to define toxicity in a quantitative way, how to begin to get some estimates of what levels are safe for an individual or a population. I have talked about air pollution and we are now prospectively looking at six cities with varying levels of air pollution. And since this is a major component of acid rain, the study in the six cities is related to acid precipitation or acid rain studies.

LEAD

Finally, we have talked about lead effects on children over many years, and we now know essentially at roughly what level of lead children can tolerate without central nervous system damage.

So I am very proud of these 20 years. I think we have done well. We look forward to the next 20 years.

Thank you again. It is a pleasure to appear before you. Our request is for $188 million, and we would be pleased to answer any questions you might have.

[Statement follows:]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of Environmental Health Sciences

The National Institute of Environmental Health Sciences (NIEHS) is celebrating this year the twentieth anniversary since its original founding as the Division of Environmental Health Sciences in 1966. We have come a long way since then.

When we now live with environmental health issues virtually every day, it is easy to forget that in 1966 the country was still reeling from the impact of Rachel Carson's Silent Spring. Twenty years ago, Dr. Irving Selikoff of Mt. Sinai had just published his landmark epidemiological studies of the hazards of asbestos. There was no Environmental Protection Agency; no Clean Water Act; no Clean Air Act, and Superfund was 15 years off. Love Canal was a modest neighborhood in New York, probably never heard of outside the Niagara Falls area. NIEHS was simply a division in the National Institutes of Health (NIH).

Since that time, with the continuing support of the Congress and this Committee in particular, we have:

--Built a cadre of scientists with unique expertise to address environ-mental health problems. At NIEHS, we have built a strong corps of scientific talent which is of worldwide repute, and which can tackle concerns from a variety of perspectives. Centers for research have been established in universities throughout the country, and individual grants and contracts have been used to create a pool of scientific talent and vital scientific information which simply did not exist twenty years ago.

--With this developing expertise, we have studied chemicals with enormous public health impact such as asbestos, lead, DES, dioxin, and PCBs. Today, we are able to estimate not only the carcinogenic potential of a chemical, but in many cases, also its effects on the reproductive, neurologic, and other systems.

Where are we going in the next ten years? Our research programs are changing to take advantage of increases in our knowledge base. We are beginning to understand more about the mechanism of action by which toxins cause disease. We can broaden our inquiry from looking at specific endpoints (carcinogenicity, teratogenicity, etc.) and specific organs of the body to looking at the whole person. We see that potentially toxic chemicals can affect all of the major systems of the body, cardiovascular, nerve, respiratory, even the immune system. These less visible effects are much more far reaching than we originally thought, and it appears that when these chemical toxins interrupt a normal process of one part of the system, they create problems in other parts of the system in ways we do not fully understand. It appears that the body is a complex communications network that cannot function properly when any one major piece is not working correctly.

In order to attack these problems, we have gradually evolved over the years into four major scientific divisions that cover the spectrum of research opportunities. Scientists in our Intramural

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Research Program (IRP) concentrate on understanding the various ways in which environmental factors enter the body and disrupt its normal functions. Using the latest techniques and equipment, they encompass many scientific disciplines as they attempt to unravel events at the cellular and subcellular level.

The Biometry and Risk Assessment Program (BRAP) utilizes epidemiological studies and mathematical models in conjunction with studies of the underlying biological mechanisms to evaluate the risks of various chemicals. BRAP also places a great deal of emphasis on the development of methodology useful in the evaluation process.

The Toxicology Research and Testing Program (TRTP) is the core of the National Toxicology Program (NTP) and through its activities provides much of the scientific information used by other regulatory and public health agencies to understand which chemicals may be public health hazards, and what types of efforts must be initiated to prevent or reduce harmful exposures.

And finally, our Extramural Program (EP) funds research and training in numerous disciplines throughout the country. Utilizing investigator initiated research grants and program projects, centers, fellowships, training grants and other mechanisms of support, a cadre of scientists at universities and research centers concentrates on the prevention, diagnosis and treatment of a variety of environmentally induced diseases.

What are some of the most promising areas of research and how are the different parts of our program focusing on them? Scientists in the Intramural Program are concentrating their efforts on understanding the mechanisms by which the environment alters the body's normal functions. The theme underlying their research efforts is based on the fact that the body's functions are fundamentally controlled by complex interactions between basic communication networks. Each of these networks or systems communicates with one another in a moment to moment, reversible fashion in response to the ever-changing set of environmental signals that act upon various parts of the body. When all is working properly, the communicating systems respond in an integrated fashion inducing adjustments in literally every part of the body down to the most minute component of each cell. At times, however, environmental insults overwhelm one or more of the communicating systems such that integration of responses becomes difficult or even impossible, leading to a debilitating disease or in some cases, if the change is irreversible, death.

Recent discoveries have pointed out how complicated these dynamics can be. NIEHS scientists have learned, for example, that manmade toxic agents such as phorbol esters and diethylstibestrol (DES) mimic the actions of many naturally-occurring, growth promoting hormones but in ways that lead to abnormal growth of cells. In intramural studies these chemicals are being used as experimental tools to broaden our understanding of the ways in which some factors increase the sensitivity of biological systems to chemical insults.

Phorbol esters, representing a class of well known tumor promoters, are counterparts to the fatty substances in our bodies that normally serve as mediators of growth-promoting hormones. However, unlike these normal body fats, they are not metabolized or deactivated by the host cell. DES formerly used as a growth stimulant in animal feed, is metabolized. Sometimes, unfortunately, its metabolism leads to the production of powerful agents called free radicals that can alter the structure and function of many cellular

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constituents, including the DNA. Such findings suggest that alterations of the levels of free radicals may be of potential usefulness for preventing the adverse effects of both man-made toxicants as well as of natural body hormones.

We will be pursuing these areas of investigation during the coming year, and I expect to be able to report our findings to you next year.

Another promising area in which our understanding is rapidly growing is the study of the molecular basis for cancer. In the last few years a family of cancer-causing genes, called oncogenes, has been uncovered. This discovery has provided tremendous insight into how a cell with altered DNA is promoted to become cancerous. It is believed that these oncogenes have a role in normal cellular growth and differentiation. However, when there is an insult to the DNA by a carcinogen, these oncogenes are activated and begin to produce altered protein products or too much of the normal product.

Drawing on NIEHS' unique capacity for carcinogenic studies in rodent model systems, we have mobilized a research effort aimed at characterizing activated oncogenes and at establishing approaches to utilize this data in analyzing the health risk from exposure to certain classes of chemical carcinogens. Our work to date suggests that oncogene activation in spontaneous tumors is different in some cases from that observed in chemically-induced tumors. This understanding provides a possible approach for substantially increasing the sensitivity of chronic animal tests for detection of carcinogens. This may help identify those cancers caused by chemicals and even some of the chemicals involved.

We are also studying the interplay among oncogenes that may occur in order for a normal cell to be transformed into a malignant one. Such work may eventually allow us to classify carcinogens according to their mechanism of action and further enhance our ability to estimate accurately the risk of cancer in humans exposed to carcinogens.

We continue to test potentially toxic compounds under the heading of the National Toxicology Program. It is a complicated process that does not always come up with the results one would have predicted or hoped for based on the experience we have gained over the years. Chlorinated paraffins, or clorowaxes, for example, had been identified as possible replacements for polychlorinated biphenyls (PCBs). The market for this class of chemicals appears to be increasing: 250,000 tons are produced worldwide each year for use as extreme pressure lubricants, flame retardants and secondary plasticizers. Among the more notable findings that have developed since I last spoke with the Committee is our awareness of the very significant toxicity of the chlorinated paraffins. The structure of this class of compounds is such that we would not have originally expected them to present as serious a hazard as the results of testing indicate. Yet, in fact, under conditions of two-year animal studies there was clear evidence of carcinogenicity.

The immediate and delayed effects of acute inhalation exposure to methyl isocyanate (MIC), the chemical reported to be the primary causative agent in the disaster in Bhopal, India, were studied in rats and mice. At toxic levels, MIC caused severe damage to the respiratory tract but no damage to other organs; however, the lung damage persisted throughout the study. Additional studies showed that there were no or minimal effects on fertility, reproduction, the immune system, and host defense. MIC was not significantly mutagenic in our tests.

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On the other hand, there is good news about ephedrine sulfate, a compound that is widely used in nonprescription pharmaceutical preparations such as nose drops, cough syrup, various ointments and suppositories, and for the relief of hemorrhoids. It is also used for the treatment of asthma and other allergic conditions. This compound was nominated for testing by the National Cancer Institute because of its widespread, long-term use. I am pleased to report that testing shows no evidence of carcinogenicity in our systems.

Last year the Committee requested from us a plan of research for studying the health effects of acid rain. That report has been submitted. It points out that acid rain is a complex phenomenon, not a toxic substance per se, that can result in increased human exposure to air pollutants and toxic metals. As such, any research plan to study the health aspects of this issue must involve a study of those pollutants and metals. NIEHS has been a major supporter of research in these areas.

A few additional areas that would more fully round out our effort in this area were identified at an NIEHS-supported conference. These new initiatives, to be funded extramurally, will involve epidemiologic studies as well as laboratory research into the synergisms and antagonisms among toxic components of acid rain, and into the potential health effects of aluminum.

Our budget request for fiscal year 1987 is $187,995,000. I would be happy to answer your questions.

RALL, DR. DAVID P.
Director, National Institute of Environmental Health Sciences
and Director, National Toxicology Program

August 3, 1926. Aurora, Illinois

Education: B.S., North Central College, 1946; M.S. (Pharmacology), Northwestern University, 1948; M.D., Northwestern University School of Medicine, 1951; Ph.D. (Pharmacology), Northwestern University, 1951.

Professional History: 1952-53, Intern, Bellevue Hospital. 1953-58, Scientist, Laboratory of Chemical Pharmacology, National Cancer Institute. 1958-63, Head, Clinical Pharmacology and Experimental Therapeutics Service, General Medicine Branch, National Cancer Institute. 1963-69, Chief, Laboratory of Chemical Pharmacology, National Cancer Institute. 1966-71, Associate Scientific Director for Experimental Therapeutics, National Cancer Institute. 1971-present, Assistant Surgeon General, USPHS.

Professional Organizations: American Association for the Advancement of Science, American Association for Cancer Research, American Public Health Association, American Society for Clinical Investigation, American Society for Pharmacology and Experimental Therapeutics, Society for Occupational and Environmental Health, Society for Risk Analysis, Society of Toxicology.

Honors, Awards: Editorial Board, Proceedings of the Society for Experimental Biology and Medicine, 1962-65. Member, National Institutes of Health Chemotherapy Study Section, 1965-67. PHS Meritorious Service Medal, 1966. Chairman, National Institute of General Medical Science Pharmacology Toxicology Review Committee, 1967-69. Editorial Board, Pharmacological Reviews, 1969-72. Chairman, DHEW Departmental Committee on Drug Research and Regulations, 1970. Associate Editor, Cancer Research, 1970-74. Chairman, OST-CEQ Ad Hoc Committee on Environmental Health Research, 1971-72. Adjunct Professor, University of North Carolina, Chapel Hill, 1972-present. US Coordinator, Environmental Health Program, US-USSR Health Exchange Agreement, 1972-present. Chairman, DHHS Committee to Coordinate Environmental and Related Programs, 1973-1985. Editorial Board, Archives of Environmental Health, 1973-76. Associate Editor, Journal of Toxicology and Environmental Health, 1974-78. DHEW Distinguished Service Medal, 1975. Member, DHEW Secretary's Review Panel on New Drug Regulation, 1975-76. Member, NAS Safe Drinking Water Committee, 1975-1977. Chairman, Committee on Health and Environmental Effects of Increased Coal Utilization, 1977-78. Member, Institute of Medicine, 1979-present. Editorial Board, American Journal of Industrial Medicine, 1980-present. Member, WHO Programme Advisory Committee, 1980-present; Chairman, 1980-81. Editorial Board, Risk Analysis, 1981-present. Editorial Board, Regulatory Toxicology and Pharmacology, 1981-present. Arnold J. Lehman Award, Society of Toxicology, 1983. Member, US Delegation to the US-Japan Cooperative Medical Science Program Committee, 1984-present.

TESTING OF CHEMICALS

Mr. **Natcher**. Thank you, Dr. Rall.

Now, as you know, you are spending about $54 million each year for testing of potentially toxic and hazardous chemicals.

What are a few of the more important findings which have come out of this effort, now just a few, and then when you get the transcript back, Dr. Rall, you may want to go into a little more detail.

Dr. **Rall**. Of the two recent ones I mentioned, methylene chloride is terribly important. Additionally, a couple of years ago, we reported that ethylene dibromide, which was in wide use and which contributed quite a bit of contamination, was seriously toxic. We have looked at a number of the dyes, red and blue dyes, which are used in foods, cosmetics and drugs. And it is interesting that we are able to segregate out those which are relatively non-toxic. Blue No. 2, for instance, is quite non-hazardous. This is important because dyes were introduced many years ago and for the most part had not had the advantage of careful testing.

We have a list of the compounds we reported out in the last three years and I will submit that for the record with comments on each one.

[Information follows:]

Attach 1.

TABLE 1. SUMMARY DATA ON NTP TECHNICAL REPORTS ON TOXICOLOGY AND CARCINOGENESIS STUDIES REVIEWED AND APPROVED BY THE BOARD OF SCIENTIFIC COUNSELORS' PEER REVIEW PANEL (JUNE 1983 -- DECEMBER 1985)

ALPHABETIC LISTING BY CHEMICAL

CHEMICAL NAME (ROUTE OF EXPOSURE)	NTP TR NO. (PEER RVW DATE)	USE(S)	LEVELS OF EVIDENCE*			
			MR	FR	MM	FM**
AMPICILLIN TRIHYDRATE (ORAL, GAVAGE)	318 (12/85)	ANTIBIOTIC	EE	NE	NE	NE
ASBESTOS, CHRYSOTILE(SR) (ORALLY WITH FOOD)	295 (07/84)	PAINT	NE	NE		
ASBESTOS, CHRYSOTILE(IR) (ORALLY WITH FOOD)	295 (07/84)	ASBESTOS CEMENT, TEXTILES, INSULATION; POSITIVE CONTROL, INTESTINAL CARCINOGEN	SE	NE		
ASBESTOS, CHRYSOTILE(IR) + DIMETHYL HYDRAZINE (ORALLY WITH FOOD)	295 (07/84)	ASBESTOS CEMENT, TEXTILES, INSULATION; POSITIVE CONTROL; INTESTINAL CARCINOGEN	IS	IS		
BENZENE (ORAL, GAVAGE)	289 (07/84)	IN GASOLINE. RAW MATERIAL FOR SYNTHESIS OF PLASTICS, RUBBER, DYES, TEXTILES, DRUGS, INSECTICIDES. SOLVENT	CE	CE	CE	CE
BENZYL ACETATE (ORAL, GAVAGE)	250 (11/84)	PERFUME FOR SOAP, FLAVORING INGREDIENT, SOLVENT FOR CELLULOSE ACETATE AND CELLULOSE NITRATE	CE	NE	SE	SE
1,3-BUTADIENE (INHALATION)	288 (10/83)	INTERMEDIATE IN THE PRODUCTION OF ELASTOMERS, POLYMERS, AND OTHER CHEMICALS			CE	CE
N-BUTYL CHLORIDE (ORAL, GAVAGE)	312 (08/85)	BUTYLATING AGENT IN ORGANIC SYNTHESIS, SOLVENT, ANTIHELMINTIC	NE	NE	NE	NE
N-BUTYL CHLORIDE (ORAL, GAVAGE)	312 (08/85)	BUTYLATING AGENT IN ORGANIC SYNTHESIS, SOLVENT, ANTIHELMINTIC			NE	NE
CHLORENDIC ACID (ORALLY WITH FOOD)	304 (08/85)	FLAME RETARDANT, MANUFACTURE OF UNSATURATED POLYESTER RESINS	CE	CE	CE	NE

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(JUNE 1983 — DECEMBER 1985)

ALPHABETIC LISTING BY CHEMICAL

CHEMICAL NAME (ROUTE OF EXPOSURE)	NTP TR NO. (PEER RVW DATE)	USE(S)	LEVELS OF EVIDENCE*			
			MR	FR	MM	FM**
CHLORINATED PARAFFINS: C23, 40% CHLORINE (ORAL, GAVAGE)	305 (08/85)	PLASTICIZER, FLAME RETARDANT AND PROCESSING AID IN CHLOROPRENE RUBBERS, ISOPRENE RUBBERS, STYRENE-BUTADIENE RUBBERS AND POLYVINYL CHLORIDE	NE	EE	CE	EE
CHLORINATED PARAFFINS: C12, 58% CHLORINE (ORAL, GAVAGE)	308 (08/85)	PLASTICIZER, SOFTENER, PROCESSING AID AND FLAME RETARDANT IN STYRENE BUTADIENE RUBBERS, ISOPRENE RUBBERS, CHLOROPRENE RUBBERS AND RUBBER BASE ADHESIVES	CE	CE	CE	CE
CHLORINATED TRISODIUM PHOSPHATE (ORAL, GAVAGE)	294 (11/84)	DETERGENT; CLEANER AND BACTERICIDE IN FOOD AND DAIRY PROCESSING	IS	IS	NE	NE
CHLORODIBROMOMETHANE (ORAL, GAVAGE)	282 (03/84)	FORMED AFTER CHLORINATION OF DRINKING WATER SUPPLIES	NE	NE	EE	SE
2-CHLOROETHANOL (ETHYLENE CHLOROHYDRIN) (SKIN PAINT)	275 (07/84)	CHEMICAL INTERMEDIATE, SOLVENT, PLANT GROWTH STIMULATOR	NE	NE	NE	NE
3-CHLORO-2-METHYLPROPENE (ORAL, GAVAGE)	300 (11/84)	PESTICIDE	CE	CE	CE	CE
CHLORPHENIRAMINE MALEATE (ORAL, GAVAGE)	317 (12/85)	ANTIHISTAMINE	NE	NE	NE	NE
C.I. ACID YELLOW 73 (FLUORESCEIN SODIUM) (ORAL WITH WATER)	265 (06/83)	DYE USED IN COSMETICS; DRUGS; TRACING WATER FLOW; DETERMINING EYE DAMAGE AND CIRCULATION TIME.	EE	NE	IS	NE
C.I. BASIC RED 9 MONOHYDROCHLORIDE (ORALLY WITH FOOD)	285 (03/85)	DYE	CE	CE	CE	CE
C.I. DISPERSE BLUE 1 (ORALLY WITH FOOD)	299 (03/85)	DYE	CE	CE	EE	NE

Insert 9c

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CHEMICAL NAME (ROUTE OF EXPOSURE)	NTP TR NO. (PEER RVW DATE)	USE(S)	LEVELS OF EVIDENCE* MR	FR	MM	FM**
DECABROMODIPHENYL OXIDE (ORALLY WITH FOOD)	309 (08/85)	FLAME RETARDANT	SE	SE	EE	NE
DIALLYL PHTHALATE (ORAL, GAVAGE)	284 (03/84)	CROSSLINKING AGENT FOR UNSATURATED POLYESTERS	NE	EE		
1,2-DICHLOROPROPANE (PROPYLENE DICHLORIDE) (ORAL, GAVAGE)	263 (06/83)	CHEMICAL INTERMEDIATE; COMPONENT OF FINISHES, DRY CLEANING FLUIDS AND PAINT REMOVERS; FUMIGANT	NE	EE	SE	SE
1,3-DICHLOROPROPENE (TELONE II) (ORAL, GAVAGE)	269 (07/84)	SOIL FUMIGANT FOR PLANT PARASITIC NEMATODES	CE	SE	IS	CE
DIMETHYL HYDROGEN PHOSPHITE (ORAL, GAVAGE)	287 (07/84)	INTERMEDIATE IN PRODUCTION OF INSECTICIDES & HERBICIDES; ADDITIVE TO LUBRICANTS; STABILIZER IN OIL & PLASTER	CE	EE	NE	NE
DIMETHYL MORPHOLINOPHOSPHORAMIDATE (ORAL, GAVAGE)	298 (11/84)	SIMULANT FOR NERVE AGENTS IN CHEMICAL DEFENSE TRAINING; NOT PRODUCED COMMERCIALLY IN U.S.	SE	SE	NE	NE
DIMETHYLVINYL CHLORIDE (DMVC) (ORAL, GAVAGE)	316 (12/85)	IN ORGANIC SYNTHESIS; FIRE HAZARD; AIR POLLUTANT	CE	CE		
DIMETHYLVINYL CHLORIDE (DMVC) (ORAL, GAVAGE)	316 (12/85)	IN ORGANIC SYNTHESIS; FIRE HAZARD; AIR POLLUTANT			CE	CE
EPHEDRINE SULFATE (ORALLY WITH FOOD)	307 (08/85)	PHARMACEUTICAL	NE	NE	NE	NE
GILSONITE (ORALLY WITH FOOD)	270 (06/83)	NATURALLY OCCURRING HYDROCARBON OF ASPHALTITE CLASS USED TO PRODUCE STOVE OILS,GASOLINE, INKS & ASPHALT	NE	NE	NE	NE
HAMAMELIS WATER (WITCH HAZEL) (SKIN PAINT)	286 (03/84)	USED IN COSMETICS	NE	NE	NE	NE

Insert

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CHEMICAL NAME (ROUTE OF EXPOSURE)	NTP TR NO. (PEER RVW DATE)	USE(S)	LEVELS OF EVIDENCE* MR	FR	MM	FM**
HC BLUE 1 (ORALLY WITH FOOD)	271 (03/84)	SEMIPERMANENT HAIR DYE	EE	SE	CE	CE
HC BLUE 2 (ORALLY WITH FOOD)	293 (07/84)	HAIR DYE	NE	NE	NE	NE
HC RED 3 (ORAL, GAVAGE)	281 (03/85)	DYE	NE	NE	EE	IS
8-HYDROXYQUINOLINE (ORALLY WITH FOOD)	276 (03/84)	REAGENT, ANTIMICROBIAL, PRESERVATIVE, CHEMICAL INTERMEDIATE	NE	NE	NE	NE
ISOPHORONE (ORAL, GAVAGE)	291 (11/84)	SOLVENT	SE	NE	EE	NE
DIESEL FUEL MARINE (SKIN PAINT)	310 (08/85)	MARINE DIESEL FUEL			EE	EE
NAVY FUELS JP-5 (SKIN PAINT)	310 (08/85)	AVIATION TURBINE ENGINE FUEL			NE	NE
DICHLOROMETHANE (METHYLENE CHLORIDE) (INHALATION)	306 (03/85)	PAINT REMOVER. AEROSOL PROPELLANT. REFIGERANT. FUMIGANT. SOLVENT. (TDB)	SE	CE	CE	CE
METHYL METHACRYLATE (INHALATION)	314 (12/85)	CHEMICAL INTERMEDIATE, DENTISTRY	NE	NE	NE	NE
MONURON (ORALLY WITH FOOD)	266 (06/83)	HERBICIDE	CE	NE	NE	NE
OXYTETRACYCLINE HYDROCHLORIDE (ORALLY WITH FOOD)	315 (12/85)	PHARMACEUTICAL	EE	EE	NE	NE
O-PHENYLPHENOL (SKIN PAINT)	301 (03/85)	FUNGICIDE			NE	NE
PROPYLENE (INHALATION)	272 (06/83)	USED IN PRODUCTION OF POLYPROPYLENE PLASTICS AND OTHER CHEMICALS	NE	NE	NE	NE

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ALPHABETIC LISTING BY CHEMICAL

CHEMICAL NAME (ROUTE OF EXPOSURE)	NTP TR NO. (PEER RVW DATE)	USE(S)	LEVELS OF EVIDENCE*			
			MR	FR	MM	FM**
PROPYLENE OXIDE (INHALATION)	267 (06/83)	INTERMEDIATE IN PRODUCTION OF POLYETHER POLYOLS; FUMIGANT FOR MEDICAL INSTRUMENTS AND FOOD.	SE	SE	CE	CE
TETRACHLOROETHYLENE (INHALATION)	311 (08/85)	SOLVENT IN DRYCLEANING; FOR FATS, OILS, TARS, RUBBER, AND GUM; AND AS METAL DEGREASING AGENT	CE	SE	CE	CE
TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDRIN) (ORAL, GAVAGE)	273 (12/85)	IN DUST SOLVENT;PRIOR: SOLVENT IN PESTICIDES & FUNGICIDES; DRY CLEANING; ANESTHETIC; CAFFEINE EXTRACTANT	IS	IS		
TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDRIN) (ORAL, GAVAGE)	273 (12/85)	IN DUST SOLVENT;PRIOR: SOLVENT IN PESTICIDES & FUNGICIDES; DRY CLEANING; ANESTHETIC; CAFFEINE EXTRACTANT	IS	IS		
TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDRIN) (ORAL, GAVAGE)	273 (12/85)	IN DUST SOLVENT;PRIOR: SOLVENT IN PESTICIDES & FUNGICIDES; DRY CLEANING; ANESTHETIC; CAFFEINE EXTRACTANT	IS	IS		
TRICHLOROETHYLENE (WITHOUT EPICHLOROHYDRIN) (ORAL, GAVAGE)	273 (12/85)	IN DUST SOLVENT;PRIOR: SOLVENT IN PESTICIDES & FUNGICIDES; DRY CLEANING; ANESTHETIC; CAFFEINE EXTRACTANT	IS	IS		
TRIS(2-ETHYLHEXYL) PHOSPHATE (ORAL, GAVAGE)	274 (10/83)	VINYL PLASTIC AND SYNTHETIC RUBBER PLASTICIZER; CHEMICAL INTERMEDIATE; FLAME RETARDANT	EE	NE	NE	SE
4-VINYLCYCLOHEXENE (ORAL, GAVAGE)	303 (03/85)	CHEMICAL INTERMEDIATE	IS	IS	IS	CE

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*CATEGORIES OF EVIDENCE (SEE ATTACHEMENT FOR DEFINITIONS):

CE = CLEAR EVIDENCE OF CARCINOGENICITY
SE = SOME EVIDENCE OF CARCINOGENICITY
EE = EQUIVOCAL EVIDENCE OF CARCINOGENICITY
NE = NO EVIDENCE OF CARCINOGENICITY
IS = INADEQUATE STUDY OF CARCINOGENICITY

** MR=MALE RATS, FR=FEMALE RATS, MM=MALE MICE, FM=FEMALE MICE

METHODS OF TESTING

Mr. NATCHER. Are you making any progress in developing cheaper and faster ways of testing chemicals, Dr. Rall?

Dr. RALL. I was a little more optimistic about this last year. At the moment I can not give you a definitive answer.

We have a very large data base now on 75 compounds which are well studied in lifetime experiments in rats and mice. We have put these 75 compounds through a whole battery of shortterm tests. The scientists right now are collating these results. We will have a preliminary meeting in May and hope to have a more definitive statement as to the value of these short-term tests by late fall. I will present this to you next year at this time.

ANIMALS IN TESTING

Mr. NATCHER. What progress has been made in developing tests which do not require the use of animals?

Dr. RALL. A large fraction of the short-term tests I just described involve the use of cells in vitro, and we are hopeful but, as I said, I am a little concerned that the short-term tests are not going to be the answer. They will be useful. We will be able to identify a series of in vitro cellular tests that can at least reduce, if not replace, the number of animals used.

CHEMICAL CAUSES OF CANCER

Mr. NATCHER. What conclusions have you reached about the extent to which cancer is caused by chemicals in the environment?

Dr. RALL. The problems of large-scale epidemiological studies which would be needed to give that sort of an answer are still essentially insurmountable.

Sir Richard Peto in Great Britain proposed a very large-scale study on lung cancer, a retrospective case control study, which would literally cost in the tens of millions of dollars. In the current climate of fiscal austerity, it does not seem possible to mount that study. I think we know of many examples of chemicals that do cause cancer in the environment, but it is currently impossible to put a number on it.

ADEQUACY OF TESTING

Mr. NATCHER. Is it true that the more than 65,000 chemicals in commercial use in the United States, fewer than 50 have been adequately tested for their ability to cause cancer in people?

Dr. RALL. That is about right. There are between 30 to 50 chemicals or processes for which the International Association for Research in Cancer say there is adequate evidence. This again points up the difficulties in using epidemiology unless the result is black and white.

It is comparitively easy, for instance, to demonstrate close correlations when an unusual cancer like mesothelioma is associated with a specific exposure to a compound such as asbestos. Or when hemangiosarcoma of the liver is found to be associated with the preceding exposure to vinyl chloride.

But the additional lung cancer associated with ubiquitous hazardous chemical compounds in the environment are very difficult to detect or correlate with specific exposures.

Mr. NATCHER. Do you agree with the estimate that 5 to 20 percent of all cancers are caused by chemical exposure?

Dr. RALL. Five to 20 percent is a wide enough boundary so that I think the real answer ought to be in there somewhere. But please do not ask me to make it any closer than that.

LOCATION OF NIEHS

Mr. NATCHER. All right, Doctor.

There was a great deal of controversy over the question of where to locate your institute before the decision was made to locate it in the Research Triangle in North Carolina.

Now that you have been there for some time, what do you find to be the chief advantages and disadvantages of being located away from Washington, D.C.?

Dr. RALL. The chief advantage, in fact an overwhelming advantage, is that we attract graduate students and young post-doctoral scientists to our laboratories. Also, our senior scientists are on the faculties of one or more than one of the local universities. We have the advantage of an academic atmosphere with an enormous pool of highly-trained scientists not only in our immediate field, but in ancillary fields. We have 50 to 100 graduate students in our institute and 70 to 80 of our scientists are on the faculty and actively teach. We have the use of summer students where we cannot only help them get their education, but they can help us. So this is an enormous advantage.

In addition, there are a number of research institutes associated with either pharmaceuticals or chemical industry associations that are within a mile or so of our institute, and the opportunities for good collaboration are unusually great and are used.

The disadvantage is that I get to spend more time on an airplane than I really like. But that applies only to me and two or three other of our top staff. And that is really about the only disadvantage.

RECRUITING OF SCIENTISTS

Mr. NATCHER. Do you have any problems recruiting and retaining scientists because of your location?

Dr. RALL. We do not because of our location. It is a very attractive place, and that is generally our selling point.

We do have some problems with keeping senior scientists because of the pay scale. This is an increasingly serious problem, particularly in recruiting senior scientists. The top level of government pay is simply no longer competitive in the research world.

FACILITIES OUTSIDE OF D.C.

Mr. NATCHER. If other institutes or agencies require additional facilities, would you recommend locating them outside of the Washington metropolitan area?

Dr. Rall. Oh, I am kind of biased because I like it in North Carolina, but I think that would be up to Dr. Malone and Dr. Wyngaarden as to whether they would want to have some other facilities scattered throughout the country. It gets a little hard to communicate closely with everybody that way.

OCCUPANCY OF NIEHS FACILITIES

Mr. Natcher. Is your new building completed and fully occupied, Doctor?

Dr. Rall. Completed and fully occupied.

Mr. Natcher. When you planned the new building, how many employees did you expect to house there and tell us, if you will, how many employees are now housed in the new building?

Dr. Rall. We expected to house about 800 to 900 people, and we currently have about that many people in the new building.

Some of them are not Federal employees; they are employees of our contractors. We have very effectively filled the space but with a slightly different mechanism than perhaps we all envisioned 10 years ago.

Mr. Natcher. How many of your employees are housed in other buildings at the North Carolina site?

Dr. Rall. Oh, we have about 250 in the so-called North Campus and about 55 in some rental space that we are trying to phase out as rapidly as we can. We need some remodeling on the North Campus to allow that 55 to move in.

EMPLOYMENT CEILINGS

Mr. Natcher. What are your employment ceilings for 1986 and 1987, and tell us, if you will, how do these compare with 1985 and 1984?

Dr. Rall. Let us just take it from '82 on.

In 1982, we had a FTE ceiling of 700, in 1983 it was 685, in 1984 it was 713, and now it is 672. And that is in fact our actual employment.

Those are the full-time equivalent figures. We have other mechanisms for temporary staff such as stay-in-schools and others so the figures I gave you a few moments ago reflect the total number of people on campus.

Mr. Natcher. And your employment as of this time, the total is what, Doctor?

Dr. Rall. Our FTE ceiling is 659 for 1986 and 1987.

Mr. Natcher. How do you plan to meet your employment ceilings for 1986 and 1987?

Dr. Rall. Well, we are over those ceilings right now. And it is going to hurt us in the area I just described as being one of the advantages in North Carolina—the students and the sort of temporary people from the universities that we work with. We are simply going to have to hire less of them, and that will take a little bit of the excitement of young minds away from our institute.

We hire young graduate scientists under the Staff Fellow Program and they are with us for three or four years. We will not be able to hire as many of those as we had planned, and that will hurt because the post-doctoral staff are among the most productive scientists in the institute.

We have followed a procedure of auditing every test to overcome the problems with one of our contractors in terms of the quality of toxicity tests. We are going to have to do a less thorough audit in the future because we do not have the people to staff that unit.

So it is going to hurt.

Mr. NATCHER. Mr. Conte, I yield to you.

ACID RAIN STUDIES

Mr. CONTE. Thank you, Mr. Chairman.

Dr. Rall, we are certainly proud and pleased to have you before our Subcommittee once again.

This year I have to say I am more pleased than usual. We finally got a plan from you, however small it is, concerning how the institute can specifically address the human health effects of acid rain. And I want to thank you personally for your efforts in focusing the institute in this particular direction.

To begin with, let me take a step backward and clear up how the institute responded in the FY 1985 to the Committee's add-on for the centers program.

With all the confusion OMB caused last year, you testified at last year's hearings that none of that additional money would go to study acid rain. Through the good work of our Chairman and this entire Subcommittee, we got the FY '85 money back, and I understand you eventually did provide additional funds to two of the centers.

Now the question is how much additional money were you able to provide for acid rain studies, and what kind of studies are we getting?

Dr. RALL. We were able to put over $400,000 into a center at NYU on health effect of acid precipitation and at Rochester on the problem with heavy metals becoming more soluble.

In addition, we have 34 projects on these pollutants, SO_x, NO_x, at about $9.5 million, and that is up some from the last year.

And, in addition, we have about $12 million on heavy metals, lead, cadmium, mercury and aluminum, a significant portion of which is involved in the health effects of acid precipitation.

So we have over $20 million potentially in this area.

Mr. CONTE. That is good.

Are those studies ongoing in '86?

Dr. RALL. Those are ongoing in 1986. We will probably have to negotiate down the renewals a little bit.

Mr. CONTE. At this point, Mr. Chairman, I would like to ask that the recent report provided by the institute for a plan to study the health effects of acid rain be printed in the record.

Mr. NATCHER. Without objection, so ordered.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

National Institute of Environmental Health Sciences

Plan for Studying the Human Health Effects of Acid Rain

Thomas E. Malone
Dr. Thomas E. Malone
Deputy Director, NIH

February 1986

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health

National Institute of Environmental Health Sciences

Plan for Studying the Human Health Effects of Acid Rain

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Plan for Studying the Human Health Effects of Acid Rain

Executive Summary

In House Report No. 99-289, the Committee on Appropriations requested that the National Institute of Environmental Health Sciences (NIEHS) develop a comprehensive plan for studying the human health effects of acid rain and that the plan include a detailed outline of the Institute's programmatic, staffing, research and funding requirements to address this problem. The following is submitted in response to that request.

In response to previous requests of the Committee, the Institute held a workshop (December 1983) and an international conference (November 1984) to determine research needed to address the human health aspects of the acid rain problem.

Research needs involve two broad areas of health concern, respiratory diseases related to inhalation of acid pollutants and potential effects of increased human exposure to toxic metals.

The NIEHS presently supports a wide range of research activities that reflect these previously determined research needs. In addition, new studies were begun in the past year regarding the identification of specific components of acid rain which are primarily responsible for lung damage.

New research initiatives will involve new epidemiologic studies, research on synergisms and antagonisms between toxic components of acid rain, and studies on the potential health effects of aluminum.

A workshop for review of the research plan will be held in 1986. An international conference is planned during the next two years.

The new initiatives are estimated to cost about three million dollars and require two positions to manage.

Plan for Studying the Human Health Effects of Acid Rain

INTRODUCTION

In its report on the Fiscal Year 1986 budget for the Department of Health and Human Services, the Committee on Appropriations stated:

> The Committee understands that a small amount of the funds added to the health science centers program in fiscal year 1985 may be used to begin to expand and initiate original research on the health effects of acid rain on humans, as the Committee requested in last year's report. The Committee is concerned with addressing this problem and therefore requests the Institute to develop a comprehensive plan for studying the human health effects of acid rain. This plan should be submitted to the Committee prior to hearings on the fiscal year 1987 budget, and should include a detailed outline of the Institute's programmatic, staffing, research and funding requirements to properly address this problem of growing national and international concern. (House Report No. 99-289, p. 70)

The following report has been prepared by the National Institutes of Health of the Department of Health and Human Services in response to this request.

BACKGROUND

In the House Appropriations report 98-357 (September 1983), the National Institute of Environmental Health Sciences (NIEHS) was asked to convene a workshop of scientists in collaboration with the Environmental Protection Agency (EPA) to assess the state of knowledge on the possible impact of acid rain on human health. In response to that request, a group of scientists was convened at the NIEHS on December 9, 1983, for a workshop and a report was subsequently submitted to the Committee in January 1984. This report has recently been published (Environmental Health Perspectives 60: 355-368, 1985) (Appendix 1). The following statement is the summary from the report:

This report summarizes the potential impact of the acid precipitation phenomenon on human health. There are two major components to this phenomenon: the predepositional phase, during which there is direct human exposure to acidic substances from ambient air, and the post-depositional phase, in which the deposition of acid materials on water and soil results in the mobilization, transport, and even chemical transformation of toxic metals. Acidification increases bioconversion of mercury to methylmercury, which accumulates in fish, increasing the risk to toxicity in people who eat fish. Increase in water and soil content of lead and cadmium increases human exposure to these metals which become additive to other sources presently under regulatory control. The potential adverse health effects of increased human exposure to aluminum is not known at the present time.

An important concept that was emphasized in the report was that acid rain is a phenomenon--not a toxic substance per se--but it can be the reason for increased human exposure to air pollutants and toxic metals. Therefore, research which addresses the human health effects of the acid rain phenomenon is not separable from investigations of the specific toxic substance involved. The acid rain phenomenon contributes to human exposure to these substances so that any consideration of the impact of the acid rain phenomenon on human health must involve a wide range of academic disciplines.

As a follow-up to the workshop, the NIEHS in collaboration with the U.S. Environmental Protection Agency (EPA) convened an international conference of scientists at NIEHS on November 15-16, 1984, to discuss the potential human health effects of acid rain. Twenty-four scientists from four countries, most of whom have conducted considerable prior research on this problem participated in the conference (see Appendix 2 for agenda). The major ojectives of the conference were to identify the body of information that pertains to the possible health effects of acid rain and to identify research needs. The papers presented at the conference were published in Environmental Health Perspectives, vol. 63, November 1985.

Research needs were addressed in terms of two major components of the acid rain issue affecting human health: (1) direct effects of acid rain on human health, particularly respiratory effects related to inhalation of acid pollutants; and, (2) indirect effects of acid rain on human health, including potential health effects of increased human exposure to toxic metals.

In addition, the report of the EPA National Acid Precipitation Program ("The Acidic Deposition Phenomenon and its Effects, Critical Assessment Review Papers," Volume II, EPA, 1983), and the report of the National Research Council on Acid Deposition, "Atmospheric Processes in Eastern North America" (1983) were consulted. Possible health effects that have been considered by others are effects on skin and eyes but, at the present time at least, there is not sufficient evidence to warrant specific attention to these topics.

DISCUSSION

The following research plan was developed as a result of discussion by the scientific staff of the NIEHS and consideration of the workshop report and of recommendations of the November 1984 NIEHS conference.

Research Needs

The primary cause of acid deposition is generally understood to be the oxidation of sulfur, nitrogen, and carbon compounds emitted to the atmosphere from natural and man-made sources. These pollutants may be removed directly from the atmosphere as dry or wet acidic deposition or may first undergo atmospheric transformations to sulfuric acid, nitric acid, and several chemical forms of particulate substances. Photochemical oxidants, such as ozone and hydrogen peroxide, and reactive volatile organic compounds known to play a role in the transformations, are also present in relatively high levels in the same geographic regions as the pollutants.

Thus, the atmospheric precursors to acid deposition involve most of the "traditional" air pollutants; namely, sulfur oxides, nitrogen oxides, particulate matter, and photochemical oxidants. Deleterious health effects have been attributed to inhalation of high concentrations of these pollutants, and numerous literature reviews and documents have been prepared on their known and potential health effects (see Appendix 1). However, it has been concluded that there is need to better establish the contribution of acid deposition to human exposure to these pollutants and the potential health effects resulting from inhaling several specific acid sulfate and nitrate components that are present in elevated concentrations in geographical regions where acid deposition is greatest. There is need for epidemiologic studies on low level sulfuric acid exposures as occur in minor periodic environmental pollution episodes (12-30 of these transient episodes occur in limited portions of eastern United States per year). And, finally, additional studies are needed to determine the minimal toxic levels of acidic pollutants (sulfuric and nitric acids, and sulfate and nitrate compounds, hydrogen ion) that produce respiratory effects in susceptible populations, such as asthmatics, people with chronic bronchitis, emphysema, etc.

Although much is known about the biologic effects of lead, cadmium, and mercury, there are large gaps in knowledge about the contribution of acidic deposition to the ecological transport (in soil, water, and living things) that results in increased human exposure to lead, cadmium, and mercury. For each of these metals, it becomes increasingly important to know the minimal levels of human exposure that produce an undesirable health effect, the factors that affect human susceptibility, and safe, effective methods for removal of excess metals from people (chelation therapy).

There is particular need for research on the influence of acid rain on the biology and possible health effects of exposure to aluminum compounds including the influence of acidity of water on speciation (chemical form of aluminum), and solubility and concentration in water. In recent years, it has been noted that an encephalopathy (brain injury) occurs in hemodialysis patients that is related to aluminum content of water, and that aluminum is present in neural tangles in the central nervous system of persons with Alzheimer disease. There are gaps in the understanding of the extent to which aluminum may play a role in the causation of the hemodialysis encephalopathy and in Alzheimer disease. There is need to identify the role of acid rain in the chemical form and transport of aluminum in human tissues, particularly across the blood-brain barrier as well as the cellular pathology of aluminum.

NIEHS-Supported Ongoing Research Activities

Through its research grants, the NIEHS presently supports a large body of research on human health effects of acidic pollutants and toxic metals in which human exposure is increased because of the acid rain phenomenon. These activities, including major recent accomplishments and research plans, are highlighted in Appendix 3.

New NIEHS-Supported Studies

Two NIEHS Environmental Health Sciences Centers have initiated additional studies with funds made available in Fiscal Year 1985. These studies are intended to identify specific components of acid rain which are primarily responsible for lung damage.

A project to be carried out at the University of Rochester will compare effects of sulfuric acid and more neutral sulfate compounds (ammonium sulfate) present in acid rain on human lungs. These studies will be conducted on human volunteers exposed to controlled levels in specifically designed exposure chambers. The objective is to determine whether lung damage due to sulfate components of acid rain is due to acidity per se or the sulfate in the compound.

The project to be carried out at the New York University is a laboratory study aimed at correlating pulmonary structural damage with deficits in lung defense mechanisms that result from acute and chronic exposure to acid sulfate and other gaseous pollutants in acid rain.

Plans for New Initiatives, Fiscal Year 1986

Review of NIEHS-supported ongoing studies (see Appendix 3) in the context of research needs that were identified in the NIEHS Conference on

Potential Health Effects of Acid Rain (November 1984) indicates that the present program supports a broad range of research activities recommended by scientists at the NIEHS workshop (1983) and conference (1984). These recommendations are detailed in the workshop report (Appendix 1) and the summary papers of the conference in Environmental Health Perspectives, November 1985.

Three additional needs are as follows: the first involves more and better epidemiological studies that relate clinical effects of exposure to episodes of acid rain. Approaches to this problem may include the correlation of excesses in hospital admissions with indices of acid rain, and levels of ambient sulfate, and ozone.

A second need concerns better understanding between synergisms or antagonisms among toxic substances involved in the acid rain phenomenon. In terms of gaseous air pollutants, specific roles of components of acidic aerosols (hydrogen ion, sulfuric acid, ammonium sulfate, and other inorganic sulfate compounds) are receiving only limited study. An essential part of this need is development of a methodology that will discern each component within the ambient environment. Synergisms and antagonism between potentially toxic metals and metabolism of essential metals are also of importance in the understanding of minimally toxic effects.

The third need concerns potential health effects of aluminum. Basic and clinical information is needed regarding effects of acidification of water on aluminum absorption, and deposition in mammalian system, and possible relationship of aluminum accumulation in body tissues to specific diseases, e.g., diseases of kidney, bone, and nervous system.

Plan for Follow-up Workshops/Conferences

Workshops or conferences will be held as a means to assure that the plan is being implemented and to initiate new research needs. A workshop is planned for late 1986.

An international conference to serve as follow-up to the international conference held at NIEHS in November 1984 will be held in 1987 or 1988.

CONCLUSIONS AND RECOMMENDATIONS

The NIEHS supports a broadly designed program that addresses the potential human health effects of the acid rain phenomenon (Appendix 3). This research is responsive to needs identified in an NIEHS-supported workshop and conference. However, there are specific areas where new research could be directed and/or expanded.

In response to recommendations of the House Committee on Appropriations, two new projects were started in 1985 directed to a specific and important gap in present knowledge: the identification of individual gaseous components of acid rain that are primarily responsible for lung damage.

Review of the current NIEHS program to study the health effects of acid rain suggests that present activities need to be continued and, in some instances, expanded. Some of these activities are longitudinal in design (Harvard Six Cities Study, description on first page of Appendix 3) and the major results of the study will occur in the future. In addition, areas of research need or gaps in the present program have been identified and plans are underway to address these needs.

Funding Requirements for New Acid Rain Initiatives

The new initiatives will be instituted by issuing Requests for Applications (RFAs). The number of new proposals resulting from RFAs that can be supported will be related to availability of funds. It is estimated that approximately three million dollars will support the peer reviewed and scientifically approved research proposals addressing the three new research initiatives: epidemiologic studies, studies identifying synergisms or antagonisms among toxic substances involved in the acid rain phenomenon, and research activities regarding aluminum toxicity. This estimate is based on the current cost of research as it relates to epidemiologic studies and laboratory research projects.

Staffing Requirements for New Acid Rain Initiatives

Because the proposed new activities will be conducted through the NIEHS extramural program, actual performance of research will be done at universities and research institutes. Two positions are required to manage an activity of this size.

Appendix I

Environmental Health Perspectives
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Potential Human Health Effects of Acid Rain: Report of a Workshop.

by Robert A. Goyer*†, John Bachmann,* Thomas W. Clarkson,* Benjamin G. Ferris, Jr.,* Judith Graham,* Paul Mushak,* Daniel P. Perl,* David P. Rall,* Richard Schlesinger,* William Sharpe,* and John M. Wood*

This report summarizes the potential impact of the acid precipitation phenomenon on human health. There are two major components to this phenomenon: the predepositional phase, during which there is direct human exposure to acidic substances from ambient air, and the post-depositional phase, in which the deposition of acid materials on water and soil results in the mobilization, transport, and even chemical transformation of toxic metals. Acidification increases bioconversion of mercury to methylmercury, which accumulates in fish, increasing the risk to toxicity in people who eat fish. Increase in water and soil content of lead and cadmium increases human exposure to these metals which become additive to other sources presently under regulatory control. The potential adverse health effects of increased human exposure to aluminum is not known at the present time.

Introduction

This report results from a request by the Committee on Appropriations of the U.S. House of Representatives that the National Institute of Environmental Health Sciences (NIEHS) convene a workshop of scientists with an interest in the area of research on possible health effects associated with acid rain exposure. The workshop was convened by the NIEHS on December 9, 1983, and was attended by both government and nongovernment scientists with expertise in various topics related to the potential health effects of the acid rain phenomenon. The resultant report is largely a review of the current information available on this topic. Specific conclusions are cited at the end of the report.

As background for these considerations, it was determined that the acid rain phenomenon has two components: the predeposition phase, which involves air pollutants, and a postdeposition phase concerning the effects of deposition of acidic substances in water or dry surfaces, including soils and buildings. The effects of the predeposition phase are sometimes referred to as direct or primary, whereas postdeposition effects are not likely to appear immediately and may be regarded as secondary or indirect. This discussion considers the immediate as well as long-term potential impact on human health from both phases of the acid rain phenomenon.

Air Pollution Precursors or Substances Contained in Acid Rain Before Deposition

The primary cause of acid deposition is generally understood to be the oxidation of sulfur, nitrogen, and carbon compounds emitted to the atmosphere from natural and man-made sources. On a global scale, natural sources (e.g., swamps, marshes, lightning) are significant, but in eastern North America an estimated 90 to 95% of precipitation acidity is thought to be related to human activities, largely the combustion of fossil fuels (e.g., power plants, industrial sources, home heating, motor vehicles) and smelting of sulfur containing ores (*1*).

The region of highest acid deposition in North America corresponds closely to the region of heavy industrialization and urbanization along the Ohio River Valley and eastern seaboard, where both anthropogenic emissions and atmospheric loadings of sulfur and nitrogen oxides are also high. These pollutants may be removed directly from the atmosphere as dry or wet acidic deposition or may first undergo atmospheric transformations to sulfuric acid, nitric acid, and several particulate species

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Photochemical oxidants, such as ozone and hydrogen peroxide, and reactive volatile organic compounds known to play a role in the transformations, are also present in relatively high levels in the same industrialized and urbanized regions.

Thus, the atmospheric precursors to acid deposition involve most of the "traditional" air pollutants; namely, sulfur dioxide, nitrogen oxides, particulate matter, and photochemical oxidants. Deleterious effects have long been attributed to inhalation of high concentrations of these pollutants, and numerous literature reviews and documents have been prepared on their known and potential health effects (*2–9*). The workshop reviewed the contribution of acid deposition to human exposure to these pollutants and the potential health effects of inhaling several specific acid sulfate and nitrate components that are present in elevated concentrations in geographical regions where acid deposition is greatest.

Atmospheric sulfates are derived principally from atmospheric transformations of gaseous sulfur dioxide. The major sulfate species occur as fine (< 2.5 µm in size) droplets or solid particles that include various mixtures of hydrogen and ammonium ions ranging in acidity from sulfuric acid to neutral ammonium sulfate. Elevated levels of sulfates occur on a regional scale throughout eastern North America and are highest in the Ohio River Valley. Multi-day events of elevated sulfate concentrations accompanied by high photochemical oxidant levels occur over large-scale regions during the summer months. Elevated sulfate events can also happen in other seasons. Although speciation data are very limited, during such events sulfuric acid equivalent levels may reach 15 to 20 µg^3 or more (*10*).

The more acidic transformation product of nitrogen oxides is nitric acid which at typical ambient humidity and temperature is present as a vapor. Based on limited measurements, ambient concentrations are generally very low, but levels as high as 10 to 20 µg^3 have been observed in the Ohio River Valley (*11*). Particulate nitrate levels (e.g., ammonium nitrate) appear to be low in eastern North America. The highest levels of both nitric acid and nitrate particles occur in western urban areas such as Los Angeles. In southern California, acid fogs have been reported in which nitric acid appears to dominate droplet acidity (*12*).

Nature of Toxic Materials Released Following Deposition

Once deposited, atmospheric acids and acid forming sulfur and nitrogen containing species do not of themselves appear to present a health threat. They may, however, indirectly mobilize toxic materials and add to total human exposure to these materials. To date, the major areas of potential concern include contamination of edible fish by toxic metals, principally mercury, soil leaching in acidified watersheds and corrosion of water and storage distribution systems, leading to elevated levels of toxic elements, chiefly lead, cadmium, and aluminum.

In general, the geographic areas in which such [illegible]creased exposures might occur are limited to the sa[illegible] regions that appear sensitive to long-term acidification of aquatic ecosystems. This includes large portions of the Northeast, portions of the Appalachian mountains and some of the upper Midwest. Areas that have usual accumulations of metals in sediments or soils and areas which lack drinking water treatment facilities may also be sensitive.

Health Effects of Air Pollutant Precursors to Acid Deposition

General Comments

The health effects of the major pre-deposition pollutants of acid rain, sulfur and nitrogen oxides, have been extensively reviewed by the National Academy of Sciences (*2–4*) and the Environmental Protection Agency (*6,7*). These reports conclude that atmospheric oxides of sulfur and nitrogen can cause human health effects. This report summarizes pertinent information in those documents and describes some of the more recently available data.

Knowledge of the effects of sulfur and nitrogen oxides is derived from three major types of studi[illegible] —epidemiology, human clinical, and animal toxicolo[illegible] Epidemiological evidence provides direct information [illegible] the responses of humans to actually encountered pollutant conditions, typically consisting of low levels of pollutant mixtures. Both acute and chronic effects can be studied. However, the complexities of human activities result in confounding factors that are not present in chamber studies with man or animals. Human clinical studies involve controlled short-term exposures of volunteers to single or, in a few cases, multiple pollutants. Data can be interpreted directly to human health risk. However, such studies are not designed to cause irreversible effects and, thus, they are very limited. With respect to animal studies, on the other hand, acute and chronic studies are possible, and effects on tissues such as the lung can be studied. Nonetheless, concentrations causing effects in animals cannot yet be directly quantitatively extrapolated to man. Therefore, optimal understanding of the health effects of these pollutants requires integrating information from all three experimental approaches.

Sulfur Oxides

Human Epidemiologic Evidence. There is little information that directly links acid precipitation with effects on human beings. Much of this has been due to the difficulties in measuring the components in [illegible] atmosphere. Frequently, the measurement has been the water-soluble sulfates without specification as to the type of sulfate present. Evidence from animal studies and limited studies on human beings in chambers do indicate that sulfuric acid for the equivalent amounts of sulfur and of sulfur particle size is more reactive biologically than ammonium sulfate or sodium sulfate. Thus it appears that it is the acidity or the hydrogen ion concentration rather than the sulfate that is the active component. There is a need to develop better methods to analyze air samples for sulfuric acid or nitric acid. Collection requires that the sample be protected from ammonia contamination which would result in measuring lower concentrations of sulfuric acid than was originally present.

There is a certain amount of data, however, that can be used to demonstrate that acid particulate matter may have an effect on human health. The episodes of high pollution in London (*13*), the Meuse Valley (*14*), and Donora, Pennsylvania (*15*), undoubtedly had high acid content in their pollution mix. The concentrations were measured during some of the London episodes (*16,17*); Hemion (*18*) estimated sulfate concentration in the Donora episode. Presumably, similar results would have been obtained in the other event. The persons most effected were the elderly, especially those with cardiovascular diseases, and young children. The concentrations associated with these episodes were high —probably in the range of milligrams per cubic meter. It was not clear which component of this pollution mix was the active agent or whether they worked in conjunction. One hypothesis held that the sulfur dioxide was absorbed into the particles and was then converted to sulfuric acid by the time it was delivered to the lung. Another held that the sulfuric acid could be directly absorbed onto the particles or formed their own aqueous droplet. In addition there may have been synergism between the soot particles and the sulfuric acid droplet.

More recent studies (*19,20*) have used sulfate as a surrogate for sulfuric acid and have presented results that suggest there may be an effect. As with virtually all of these studies, there has been considerable confounding of the effects of one pollutant with other pollutants and it has been virtually impossible to isolate which component was the active one or whether they were acting in concordance.

The Community Health and Environmental Surveillance System (CHESS) studies (*20*), although severely criticized, did draw more attention to the possible effects of acid sulfates. Earlier, Waller and Lawther (*21*) had suggested that sulfuric acid was an active ingredient in the London fogs.

Thus, there is suggestive evidence that sulfates or, more specifically, acidic sulfates can have an effect on health. The evidence from epidemiologic studies is weak due to the confounding factors. Better information as to the effect of sulfuric acid comes from human and animal exposure studies.

In at least one of the on-going Harvard Six Cities epidemiologic studies, efforts are being made to measure sulfuric acid and ammonium sulfates. Thus far only a couple of cities have been monitored. The others will be included later after the initial field testing of the instruments has proven to be satisfactory.

Controlled Chamber Studies with Humans and Experimental Animals. Standard tests of lung mechanics have been used most often as criteria of irritancy potential due to inhaled sulfur oxide aerosols. However, attempts to produce significant changes in respiratory function of resting healthy humans and experimental animals, with the possible exception of the guinea pig, with submicrometer aerosols at concentrations of up to 1 mg/m^3 for up to 1 hr were largely unsuccessful (*22–27*). With exercise, a slight depression in some indices was noted after a 2-hr exposure to 1 mg/m^3 sulfuric acid (*28*). Using bronchial provocation testing following acid sulfate exposures for 16 min at 1 mg/m^3, Utell et al. (*29*) showed a potentiation of human response to carbachol challenge in relation to aerosol acidity, i.e., sulfuric acid > ammonium bisulfate > sodium bisulfate > ammonium sulfate. A few studies have examined responses in people with extrinsic asthma; results are contradictory. Avol et al. (*30*) noted minor changes in pulmonary resistance in two of six asthmatics exposed to 0.075 mg/m^3 (0.3 μm) sulfuric acid for 2 hr. Sackner and Ford (*31*) found no changes in lung mechanics in adult asthmatics exposed to sulfuric acid at 1 mg/m^3 (1.5 μm) for 10 min, while Spektor (*32*) found changes in some indices due to 1-hr exposures to a submicrometer aerosol at the same concentration, and Utell et al. (*29*) noted changes in specific airway conductance after exposure to sulfuric acid at 0.45 or 1 mg/m^3 for 16 min. Most recently, Koenig et al. (*33*) noted significant alteration in lung mechanics of adolescent asthmatics after exposure for 30 min at rest plus 10 min with exercise to 0.1 mg/m^3 sulfuric acid.

Another aspect of lung physiology which has been examined is clearance function, which is involved in lung defense. Decreased ciliary beat frequency was observed in tracheal explants obtained from hamsters exposed for 2–3 hr to submicrometer amounts of sulfuric acid (0.88–1.1 mg/m^3) (*34,35*). Effects upon tracheobronchial mucociliary clearance function in intact animals, which is a more sensitive index than mechanical function, have been reviewed recently by Schlesinger (*36*). Transient clearance rate alterations have been noted in humans and experimental animals following 1-hr exposures to submicrometer amounts of sulfuric acid at 0.095–0.1 mg/m^3 (*25,36,37*). Levels of 1.7 mg/m^3 ammonium sulfate were required for similar responses (*36*) in experimental animals, and no changes have been found for ammonium sulfate at 3–3.6 mg/m^3 for 1–4 hr (*38*).

Transient changes may become long-lasting. Schlesinger et al. (*27*) demonstrated persistently slowed clearance in two of four experimental animals (donkeys) after six individual 1-hr exposures to sulfuric acid at 0.2–1.0 mg/m^3. Subsequently, four animals were exposed 1 hr daily, 5 days/week to sulfuric acid at ~ 0.1 mg/m^3. Within the first few weeks of exposure, all four developed erratic clearance rates, while two developed persistently slowed bronchial clearance during the second three months of exposure and during four months of follow-up measurements.

Because persistent clearance alteration is seen in chronic bronchitis, sulfuric acid has been hypothesized as having a role in pathogenesis of bronchitis. Although direct evidence for an association between sulfuric acid and chronic bronchitis is lacking, this hypothesis is strengthened by comparing studies with submicrometer amounts of sulfuric acid and whole fresh cigarette smoke exposures with donkeys and humans *(40)*; cigarettes are involved in the etiology of human chronic bronchitis. The effects of both agents on mucociliary clearance are essentially the same in terms of transient acceleration of clearance in low dose exposures, transient slowing following high doses, and alteration in clearance rate persisting for several months following multiple exposures. A recent study by Schlesinger et al. *(41)* adds further support. Rabbits exposed to sulfuric acid at ~0.25–0.5 mg/m for 1 hr/day, 5 days/week, for four weeks demonstrated an increase in secretory cells in the epithelium of small airways, a hallmark of chronic bronchitis. In addition, in some cases, the epithelium was thickened and airway diameters were narrowed.

Clearance from the respiratory airways is mediated by alveolar macrophages, which are also responsible for the lung's bacteriocidal function. Few data exist on effects in this region: and available studies use unrealistically high levels of acid sulfates. Mice exposed to small amounts 80, 150 or 300 mg/m^3 of sulfuric acid for 3 hr showed enhanced mortality due to a subsequently inhaled bacterial aerosol only at the highest concentration, and this was probably due to tissue damage *(42)*; no change was noted in the numbers of macrophages in lavage fluid. Macrophages harvested from mice exposed to sulfuric acid from 125 to 154 mg/m^3 from 10–14 days showed decreased interferon titers in their culture fluid *(43)*. In the only study of effects upon alveolar clearance in intact animals *(38)*, rats exposed for 4 hr (at 39% R.H.) to 3.6 mg/m^3 sulfuric acid exhibited clearance deceleration 2–17 days after exposure, a phase mediated by macrophages.

There are few investigations of the chronic effects of sulfates and these have only been reported with sulfuric acid. Most were conducted at a time before highly sensitive quantitative measurement techniques for lung morphology were available. Interpretation of the studies is made difficult because whole body exposures were used, thereby permitting an uncontrolled neutralization of sulfuric acid within the chamber atmosphere. Therefore, sulfuric acid concentration response effects cannot be determined with precision.

Guinea pigs were unaffected by a one-year exposure of up to 0.9 mg/m^3 sulfuric acid *(44,45)*. Monkeys experienced a transient alteration in pulmonary function during a one and one-half year exposure to submicrometer, but not larger, sulfuric acid at 0.4–0.5 mg/m^3 *(44)*. Lung structure was also changed by som[illegible] the sulfuric acid concentrations; a typical finding [illegible] thickening of the walls of respiratory bronchioles. However, the responses were not consistently relatable to concentration or particle size of sulfuric acid. Lung structure of dogs was not affected by about one and one-half years of exposure to 0.9 mg/m^3 sulfuric acid, although there were some changes in pulmonary function *(46,47)*.

Chronic effects of ammonium sulfate are unknown. Recent subchronic studies (exposures of 5 days/week for 4 weeks) have shown that ammonium sulfate is not as innocuous as presumed from acute exposure studies *(48)*. A level of 1 mg/m^3 ammonium sulfate caused structural and functional changes in the lungs of rats, and to a lesser degree in guinea pigs. Those animals with laboratory-induced emphysema appeared to be more resistant.

The interaction of sulfuric acid with other particles has been the subject of several studies. Sulfuric acid did not potentiate the effects of ozone, nitrogen dioxide, or sulfur dioxide in normal human subjects exposed acutely *(49)*. Guinea pigs exposed to various combinations of sulfuric acid, sulfur dioxide, and fly ash for one year experienced no changes in pulmonary function or structure *(45)*. Monkeys exposed for one and one-half years to similar combinations having about 0.9 mg/m^3 sulfuric acid had no alterations in pulmonary function. Howev[illegible] lung structure was altered. Fly ash did not enhance [illegible] effects of sulfuric acid.

The most extensive interaction study was conducted with dogs exposed for about five and one-half years to 1.1 mg/m^3 sulfur dioxide plus 0.09 mg/m^3 sulfuric acid and then allowed to remain in unpolluted air for about two and one-half years *(50)*. Periodic examinations were made, and some changes in pulmonary functions were noted throughout exposure. The functional losses continued following the termination of exposure. Morphometric measurements of the lungs were made at the two and one-half year post-exposure period *(51)*. Several types of changes were observed. The most noteworthy were changes that the authors considered analogous to an incipient stage of human centrolobular emphysema.

The only significant body of data for the interaction of sulfuric acid with gases involves ozone. Generally, the results of these studies are dependent upon the biological system examined and the exposure regimen utilized. Last and Cross *(52)* found synergistic effects of 1 mg/m^3 sulfuric acid and 0.4–0.5 ppm ozone on glycoprotein synthesis (an index of mucus production) in rats. Antagonistic effects on ciliary beating frequency were observed when hamsters were exposed in sequence, first to 0.1 ppm ozone and then to 0.9 mg/m^3 sulfuric acid *(34)*. Gardner et al. *(53)* showed additive effects of 0.9 mg/m^3 sulfuric acid and 0.1 ppm ozone for susceptibility to bacterial lung infections of mice exposed [illegible] sequence to ozone first.

Nitrogen Oxides

There are virtually no epidemiologic, human clinical, or animal toxicological studies that have examined the effects of nitric acid. Very few data exist concerning response to inhaled particulate nitrogen oxides; those that are available relate most solely to pulmonary mechanics. Dogs exposed to sodium nitrate at 10 mg/m (0.1 µm) for 7.5 min or sheep exposed to 5 mg/m for 4 hr showed no significant change in lung mechanical function (*54*). Similar negative results were obtained in healthy human subjects exposed to sodium nitrate at 1 mg/m for 10 min (*54*) or in healthy and asthmatic adults exposed for 2 hr (with intermittent exercise) to ammonium nitrate at 0.2 mg/m (1.1 µm) (*55*). In a study by Utell et al. (*29*), no significant enhanced effect of a carbachol (bronchoconstrictor) challenge was observed in either a group of normals or asthmatics previously exposed to sodium nitrate at 7 mg/m (0.46 µm) for 16 min; however, two asthmatics did show mild potentiation of the carbachol-induced bronchoconstriction after sodium nitrate exposure. Normal and allergic sheep exposed for 4 hr to 1.6 ppm nitric acid vapor showed no change in pulmonary flow resistance (*56*). With bronchial provocation testing, no significant change in airway reactivity was noted in the normal animals, but mild hyperactivity occurred in allergic sheep within 24 hr after exposure.

Stutts et al. (*57*) found that ammonium nitrate could alter sodium and chloride transport across canine tracheal epithelium. However, the response was ascribed to ammonium ion rather than nitrate ion since sodium nitrate had no effect.

Health Effects That May Occur During the Postdepositional Stage of Acid Rain

General Comments

Several steps are involved in the postdepositional stage of acid rain, so that the potential effects on health resulting from changes occurring during this stage are sometimes referred to as indirect effects. The steps in the postdepositional stage include mobilization of metals from generally fixed sites, such as ores and insoluble deposits, to media that contribute to human exposure, such as water and food, and transformation to more toxic forms (alkylation of mercury to methylmercury). Considerable attention and research have focused on the ecological changes that are involved in the acidic postdeposition stage, including effects on soil systems, vegetation, aquatic chemistry and aquatic biology, particularly the impact on reproduction and growth of fish. These effects are well documented in other major studies, such as the Report of the National Academy of Sciences on Acid Rain Deposition (*7*). It may be argued that effects on soil that influence the ability to grow food crops, effects on crops themselves, and reduction in consumable fish are, in themselves, indirect threats to human health. However, the level of such effects is not sufficient to support such an argument. In fact, no effects on human health have been demonstrated to date to be the result of the sequence of changes that occur during the postdepositional stage of the acid rain phenomenon. The lack of documented effects may reflect that no such effects exist or that interest in the phenomenon of acid rain is recent; few, if any, investigations of possible linkages have been made. In principle, acid rain in the postdeposition stage may influence human exposure to toxic chemicals by two main routes: the accumulation of chemicals in food chains and the contamination of drinking water. Metals are the substances primarily affected, particularly lead, cadmium, mercury, and aluminum.

Mobilization of Metals during the Postdeposition Stage

Williams (*58*) had pointed out that metal ion interactions in biology can be divided into three classes: metal ions in fast exchange; metal ions in intermediary exchange; and metal ions in slow exchange. These changes occur with organic ligands to which metal ions can coordinate. Metal ions in fast exchange are especially important in toxicity considerations. Examples of elements in fast exchange in biology are the alkali metals, sodium and potassium, and the alkali earth metals, calcium and magnesium, as well as the most important hydrogen ion. Solid-state ions of the elements lead, cadmium, and aluminum can be replaced by any of the ions in fast exchange, especially by hydrogen ion, to cause their solubilization in water. This process can make lead, cadmium, and aluminum soluble and available for bioconcentration in food chains and in drinking water sources to which humans are exposed. This must be considered in terms of total exposure to aluminum and aluminum compounds.

In acidic lakes, aluminum is of special concern because it is very abundant in sedimentary rocks (i.e., over 5%). In fact, this element is more abundant than iron in the earth's surface (*59,60*). Acid rain provides the increase in hydrogen ion concentration, which in turn increases the concentrations of soluble aluminum containing chemical species in water. Furthermore, absorption and neurotoxicity of aluminum are enhanced by low dietary calcium and magnesium (*61*). Acidic soils are often deficient in these alkaline earth metals.

The bioaccumulation of mercury occurs in acid lakes by an entirely different mechanism. Inorganic chemistry is introduced as a result of atmospheric deposition. Once present in soils and sediments, such inorganic complexes of mercury are biomethlylated to give the neurotoxins methylmercury and dimethylmercury. Methylmercury is produced in sediments and soils under acidic conditions, whereas dimethylmercury is produced under alkaline conditions. The details of this mercury cycle are very well understood at the biochemical level. Most of the chemical species of mercury, which are present in acid lakes, have been detected and analyzed by sophisticated analytical techniques. This is not true for the analysis of aluminum species where the predominant chemical species in acidic waters and in biota are not yet understood.

Mercury

Toxic Effects of Methylmercury in Man. The human toxicology of methylmercury is well described in the literature due to catastrophic poisonings (fish) in Japan in the 1950s and 1960s and to a large poisoning (treated seed) in Iraq in the winter of 1971–72. Studies on a number of cases of industrial poisoning have also contributed substantially to the understanding of the toxic effects of methylmercury on man (62), primarily the damaging of the nervous system. The main areas affected are associated with the sensory, visual, and auditory functions and those areas concerned with coordination, especially the cerebellum. The earliest effects are nonspecific symptoms, such as complaints of paresthesia, malaise, and blurred vision. Subsequently, signs appear such as concentric constriction of the visual field, deafness, dysarthria, and ataxia. In the worst cases, the patient may go on to coma and ultimately death. In less severe cases, some degree of recovery occurs in each symptom; this is believed to be a functional recovery that depends on the compensatory function of the central nervous system. The subjective complaint of paresthesia was found to be a permanent symptom with patients exposed in the Japanese outbreak, whereas in the Iraq outbreak, paresthesia in many cases was transient. The reason for the difference is not known.

Dose-effect and dose-response relationships for methylmercury compounds in man have been presented and evaluated previously (63,62). The most recent analysis of the Iraq data has been published by Nordberg and Strangert (64–66). This analysis took into account not only the individual range of thresholds to such symptoms as paresthesia but also the interindividual variation in whole body biological half-times. These two distributions were combined to give an overall estimate of the risk of paresthesia for a given steady state daily intake of methylmercury. Their calculations indicated that an intake of 50 µg/day in an adult person gives a risk of about 0.3% of the symptom of paresthesia, whereas an intake of 200 µg/day would give a risk of about 8% of symptoms of paresthesia.

The range of individual intakes of methylmercury in the United States is not known. With reference to Table 1, a Pike consumer would need to ingest about three times the average amount to approach a daily intake of 50 µg mercury assuming an average mercury level in Pike of 1 µg Hg/g wet weight. However, these estimates of risk apply only to adults. Observations on both human subjects and experimental animals indicate that the developing central nervous system is more sensitive to damage from methylmercury than the adult nervous

Table 1. Fish and shellfish consumption in the United States (September 1973-August 1974).a

	Rank	g/yr	% of total by weight	Number of actual users (millions)	Mean amount per user, g/day
Total		2687	100.0	197	18.7
Tuna (mainly canned)	1	634	23.6	130	6.1
Unclassified (mainly breaded, including fish sticks)	2	542	20.2	68	10.0
Shrimp	3	401	14.9	45	5.3
Ocean perch^b	4	165	6.1	19	9.7
Flounder	5	131	4.9	31	8.6
Clams	6	118	4.4	18	7.6
Crabs/lobsters	7	112	4.2	13	10.6
Salmon	8	101	3.8	19	6.7
Oysters/scallops	9	85	3.2	14	7.8
Trout	10	88	3.3	9	12.3
Cod^b	11	78	2.9	12	8.1
Bass^c	12	73	2.7	7.6	12.0
Catfish^c	13	70	2.6	7.5	12.1
Haddock^b	14	63	2.3	11	8.6
Pollock^b	15	54	2.0	11	6.8
Herring/smelt/ Sardines	16	48	1.8	10	6.7
Pike^c	17	32	1.2	2.5	17.4
Halibut^b	18	30	1.1	3.0	8.0
Snapper	19	30	1.1	4.0	9.3
Whiting	20	22	0.8	2.2	9.7
All other classified		137	5.1		

aEPA data.
bMainly imports.
cFreshwater.

system. The first indications came from the outbreak of methylmercury poisoning in Minamata, Japan, in the 1950s, when it was found that mothers who were slightly poisoned gave birth to infants with severe cerebral palsy (*67*).

Subsequent studies on animals confirm the increased sensitivity of the fetus. In the Iraq outbreak in 1971–72 cases of severe damage to the central nervous system in infants prenatally exposed were also reported. More recent follow-up studies in Iraq have indicated a milder syndrome at lower exposure levels. In fact, it has been possible to demonstrate a relationship between the maximum hair level in the mothers during pregnancy and the frequency of abnormalities in their infants.

The clinical picture was dose-dependent. In those who were exposed to high maternal blood levels of methylmercury, the picture was of cerebral palsy indistinguishable from that caused by other factors. Microcephaly, hyperreflexia, and gross motor and mental impairment sometimes associated with blindness or deafness was the main pattern (*68*). Milder degrees of the affliction were not easy to diagnose during the first few months of life but they became clear with later times. The cases showed mainly psychomotor impairment and persistence of pathological reflexes. The mildest cases had findings quite similar to the findings in the minimal brain damage syndrome (*68*). The frequency of mental retardation in infants may be correlated with maximum hair levels in the mother. Effects are detectable in prenatally exposed infants with maternal hair levels substantially lower than those associated with the onset of signs in adults.

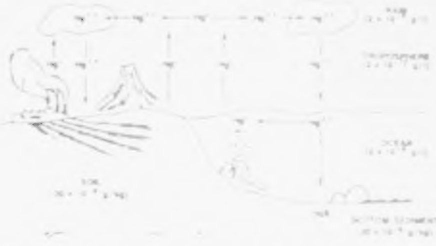

FIGURE 1. A schematic representation of the global cycle of mercury. The scheme is based on [illegible] and Lindqvist et al. [illegible]

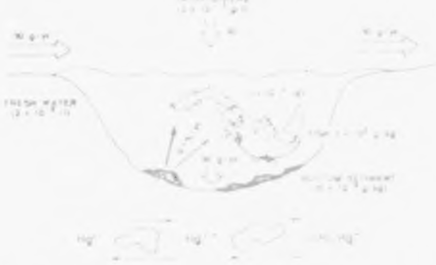

FIGURE 2. A schematic representation [illegible] (68).

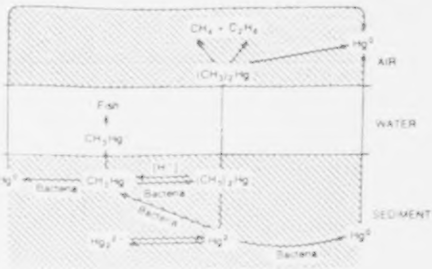

FIGURE 3. A biogeochemical cycle involving bacterial methylation and demethylation of mercury. Adapted from Fig. 3.1 of NAS (70).

Role of Acid Precipitation in Mobilization and Transformation of Mercury to Methylmercury. There is mounting evidence that acid precipitation leads to higher levels of methylmercury in edible tissues of freshwater fish (*69*). To appreciate the mechanisms that underly this linkage, it will be useful succinctly to summarize the fate of mercury in the environment. Two cycles are involved: one is global in scope and inorganic in nature; the other cycle is local and biological. The global cycle (Fig. 1) involves the emission of elemental mercury vapor from land and water surface and from anthropogenic sources, especially coal-burning power stations. The anthropogenic contribution (of the order of 3000–5000 tons per year) is probably about 25% of the total emission to the atmosphere. Long distance transport of the elemental vapor occurs in the atmosphere. Its residence time is on the order of years. A small fraction of the mercury in the atmosphere is in the water-soluble form. Its precise chemical species is not yet known. This form is returned to the earth's surface in rain water and possibly by dry deposition. Its residence time is of the order of a few days. Bodies of fresh water will receive soluble mercury directly from the atmosphere and indirectly from water run-off from land. A balance study on Swedish lakes indicated the direct and indirect contributions were about equal (Fig. 2). In the water phase, the soluble mercury may be reduced back to metallic mercury and evaporate to the atmosphere. The remainder attaches to sediment. At this point the biological cycle operates on mercury. Inorganic mercury attached to sediment becomes a substrate for microorganisms that produce mono- and dimethylmercury (Fig. 3). The monomethyl species is avidly accumulated by fish and increases in concentration at higher trophic levels of the aquatic food chain (Fig. 3). Concentrations of methylmercury are highest in the tissue of large predatory fish such as northern pike, lake trout, and bass. The levels of methylmercury present in the water phase are extremely low, probably less than 10^{-11} g/L, whereas the concentration in muscle of northern pike may be as high as 10^{-3} g/kg representing a large bioconcentration factor of one hundred millionfold.

Investigators in Sweden noted unusually high concentrations of mercury in pike in lakes that did not receive any known direct discharge of mercury from anthropogenic sources. Furthermore, the level of methylmercury in fish tissue was statistically correlated with the pH of the water. In the pH range of 5–7, the methylmercury in fish rose as the pH fell. In extremely acidic water, below pH 5, lower mercury levels were seen (Fig. 4). Studies in other countries affected by acid rain, e.g., Norway and Canada, have also noted fish in acidic water tend to have higher methylmercury levels.

Many factors are believed to influence methylmercury levels in fish of which pH is only one. The mechanism of the pH effect is not yet fully understood. Several possible mechanisms have been suggested: acidic precipitation may remove mercury from the atmosphere more effectively than neutral pH. The rate of methylation of inorganic mercury by microorganisms is pH dependent, with the maximum rate formation of monomethylmercury occurring at lower than pH 6. The pH influences the species of methylmercury formed by microorganisms, a higher pH favoring the formation of the insoluble and volatile dimethylmercury which would not be accumulated readily in fish but rather vaporized into the atmosphere (Fig. 3). A reduced pH should favor the presence of a divalent ionic mercury in water, reducing its presence in complexes and chelates, and therefore making mercury more available for methylation reactions. The total biomass in an acidic lake is usually lower than in a neutral lake. Thus, since most of methylmercury is present in the biomass, one would expect its concentration to be necessarily higher in the biomass (including the fish) in the acidic lake.

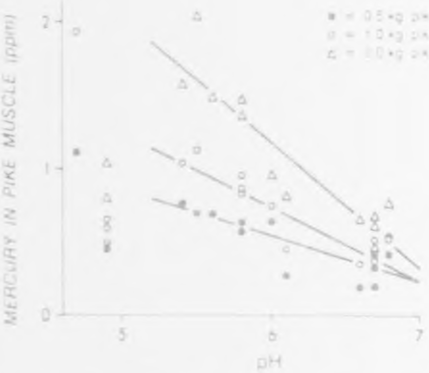

FIGURE 4. The concentration of [illegible] in pike muscle [illegible] as a function of pH. Regression lines [illegible] the three groups of fish [illegible] 0.5, 1.0 and 2.0 kg over the pH range 5 to 7. Adapted from [illegible] No. 192 [illegible].

The consequences of elevated methylmercury levels in freshwater fish may be evaluated from two points of view. First, the current Federal and state guidelines will be enforced, thereby leading to the blacklisting of lakes and rivers having unacceptably high concentrations of mercury in fish. This has occurred in Scandinavia, where there is a Federal action level of 1 μg Hg/g wet weight of fish muscle—the same as the level of the U.S. Food and Drug Administration. The second viewpoint is that human intake of methylmercury will increase. Fish and fish products are the dominant if not only sources of human intake of methylmercury.

The U.S. Department of Commerce (*70*) conducted a survey of over 25,000 individuals representative of the U.S. population with the intention of determining the intake of methylmercury from fish. On a per weight basis, consumption of tuna far exceeds that of other species of fish in the U.S. (Table 1). However, since the actual number of users or consumers of tuna fish is also very high, the amount of tuna consumed per user is not dramatically different than the consumption per user of other species of fish. It is of interest to note that the species with highest consumption per user is northern pike, having a value of 17.4 g/day; species of freshwater fish, catfish, bass, and trout are next highest in per user consumption at about 12 g/day.

Lead. Lead is probably the most ubiquitous toxic metal, and its distribution in the environment, particularly its presence in media that contributes to human exposure, air, water, food, is in large part the result of man's activities. It is clear that the acid rain phenomenon contributes to this problem in a number of ways, but the relative significance of acid rain in a quantitative sense is not yet certain.

Toxicity of Lead. A number of chronic subtle and overt biological effects of lead in humans have been well studied and documented. These include effects on heme biosynthesis and erythropoiesis, central and peripheral nervous system toxicity, kidney effects, derangement of Vitamin D metabolism, and essential trace metal metabolism such as iron, calcium, and zinc. However, it is not possible to quantitate human toxicity risk for lead due to long-term acid precipitation simply because it is not possible to quantitate the potential increase in lead exposure attributable to this factor. But it is possible rank the various effects of lead across a gradient of increasing human exposure, as indexed by some biological measure such as blood lead, and, if we are at some time able to identify the contribution of the acid rain phenomenon to increases of lead in the environment, we might then be able to measure the impact of the acid rain phenomenon on the human health effects of lead.

Ranking of health effects of lead must be done with that segment of the U.S. general population at most risk for the adverse effects of lead: preschool children. The threshold for effects of lead occur generally at a lower index of exposure in preschool children than adults (71,72). These apparent "thresholds" or lowest observable effect levels are given in Table 2. While basic understanding of some of these effects is still under study, it can be seen that more than one effect may occur at even moderate levels of lead exposure. Furthermore, pediatric population surveys, such as the National Health and Nutrition Evaluation Survey (NHANES II), have shown that there are relatively large numbers of children, particularly those in urban areas, whose blood lead values are at or approaching some of the threshold categories in Table 2 (73). For example, NHANES II tabulations show that 45.2% of black children aged 6 months to 5 years have 20–29 µg Pb/dL of blood, 9.2% have 30–39 µg Pb/dL, and 1.7% have values higher than 40 µg Pb/dL. It is clear from Table 2 and these percentage distributions that the superimposing of any additional lead exposure factor, such as any due to the acid rain phenomenon, will have a significant impact on these percentages by shifting children to higher exposure categories.

Contributions of Acid Rain to Exposure of Children to Lead. The general population, including pregnant women and children, receives its major exposure to lead through lead content of food and water. In addition, children are further exposed to significant amounts of lead in soil, dust, and paint because of their behavioral relationships to these sources, e.g., hand-to-mouth contamination. Acidification of drinking water increases the solubility of lead in the water. More than half of the U.S. population living in year-round dwelling units receive its drinking water from municipal or private supplies derived from surface and ground water (74). Lead may be mobilized from sediments and soils to bodies of water which may serve as sources of drinking water. Davies and Everhart (75) have calculated that lead solubility in soft, acidic water can reach potentially toxic levels, e.g., 500 µg Pb/L, while Lazrus and coworkers (76) estimated that soft waters could mobilize significant levels of lead in surface runoff in the northeastern U.S. at values of pH which are presently attainable from acid precipitation in this area of the U.S.

Relatively acidic water entering a plumbing system prevents the buildup of a normally protective calcium carbonate plaque in plumbing and permits ongoing dissolution of lead. This problem is most acute in older urban areas of the U.S. such as New England where lead piping itself may be in use (77), but will also exist to some degree with copper plumbing having lead solder for sealing of joints (78). A sizable data base exists for assessing potential impact of acidic drinking water. Studies of the problem in Glasgow, Scotland, where

Table 2. Lowest observable effect levels in young children for lead.a

Lowest observed effect level (blood lead, µg Pb/dL)	Effect observed	Significance
<10	ALA-D inhibition Py-5'-N inhibition	[illegible]
15–20	EP elevation	[illegible]
10–20	[illegible]	[illegible]
15–20	[illegible]	[illegible] for potential [illegible]
40	Reduced [illegible]	[illegible] nervous system dysfunction
40	[illegible]	[illegible] impairment
		[illegible]
80 and above	[illegible]	[illegible]

a Abbreviations: [illegible]

levels of lead in drinking water can reach 500 μg Pb/L because of soft, acidic water and lead plumbing, have shown that these levels of exposure can be toxic (79,80).

A further consideration with acid precipitation is the corrosive effect or deterioration or weathering rate of outside surfaces containing paint of high lead content. This weathering process is not restricted to deteriorated housing in inner urban areas of the U.S. but can also occur in rural areas as well. It is known that significant external weathering of painted surfaces over time is an active process (81,82), and there is potential for acid precipitation in hastening this process with concomitant transfer to soils and dusts in contact with children, since a common ingredient in high lead paint is basic lead carbonate.

Finally, it must be emphasized that children take in more lead than adults on a unit weight basis, absorb more of the intake, and also retain a higher percentage. Hence, drinking water used in formulae or other food preparation, as well as beverage, would pose a proportionately greater impact on this age group in terms of lead content changes associated with acid precipitation.

Cadmium

Cadmium Toxicity. The major adverse human health effect associated with long-term low level ingestion of cadmium is renal disease (83). Although inhalation of cadmium is known to cause lung disease and possibly cancer of the lung, the potential contributions of cadmium to body accumulations are more likely to be by ingestion and not inhalation. Current understanding of cadmium toxicity is that nearly all cadmium ingested over a lifetime is retained; the biological half-time is probably more than 30 years. Accumulation is greatest in renal cortex and it has been learned from exposed human populations and experimental animals that kidney disease may occur when a critical level of cadmium is reached in the kidney cortex. The actual level in the kidney that causes disease and the mechanism or pathogenesis of the disease is still being studied, but much is known. Another factor in the cadmium problem is that there is no acceptable method for removing this metal from the body as there is for most other toxic metals. Therefore, from a public health viewpoint, it is prudent to be particularly concerned about activities that will add to human exposures.

Role of the Acid Precipitation Phenomenon on Human Exposure to Cadmium. Those segments of the U.S. population at increased risk to the adverse effects of cadmium are the elderly, cigarette smokers, and individuals with unusual dietary habits, particularly vegetarians. Cadmium, like lead, is an element which accumulates in the human body. Unlike lead, however, this accumulation is only associated with vital organs such as the kidney and it is thus difficult to forestall adverse effects due to such accumulation by other than a policy of exposure prevention. Cadmium, therefore, epitomizes an agent whose control is of necessity a prospective process, and the impact of long-term acid precipitation needs to be considered this.

There are at least three routes for long-term impact of acid precipitation on human exposure to cadmium which should be considered. As with lead, relatively acidic water in plumbing systems has the potential to mobilize cadmium from soldered joints of copper plumbing. While the degree of this problem is not that of lead (see above), available data support the notion that it can be a cadmium exposure risk factor. For example, Deane et al. (84) reported that 7% of households studied in Seattle had tap water cadmium levels which exceeded the U.S. Public Health Service standard of 10 μg/L for cadmium. The Seattle water supply is quite soft. A potentially greater problem may reside in the mobilization of cadmium from crop soils which are dressed with cadmium-containing phosphate fertilizer into various crops because of the long-term impact of acid precipitation on such lands. The crops include not only food categories but other economically important production, particularly tobacco. Tobacco and leafy food vegetables are particularly effective scavengers of soil cadmium under conditions of reduced pH. The amount of land involved is very large and there are presently no regulatory guidelines for the use of cadmium-containing phosphate on such lands (85). A third consideration relates to the land application of municipal sewage sludges, which is increasingly being viewed as a disposal option of last resort (85). While regulation attending such land spreading include liming to immobilize the cadmium and other toxic elements, the long-term impact of acid precipitation on these control measures can be deleterious. An additional factor is the potential for leaching of cadmium from waste dumps.

Aluminum

Aluminum, the most common metallic element, comprises 5% of the earth's crust. For the most part, aluminum is largely present in insoluble, and thus biologically unavailable, forms. Among the effects of acid rain is the solubilization of significant amounts of aluminum from the soil resulting in increased levels of the element in local lakes and streams. The possible toxic effects of these elevated aluminum levels on fish and vegetation has been the subject of research and there is evidence available that in this setting it can indeed exert a harmful effect on both flora and fauna. In the present state of scientific knowledge, we cannot make any definitive statements as to the potential human health effects of acid rain with respect to aluminum.

Aluminum is not known to be utilized in any natural biologic process and is generally considered to be relatively nontoxic to man. However, within the past several years, aluminum has been implicated in th pathogenesis of several human disorders. Most of the conditions occur in patients with chronic renal failure. The best characterized is a condition referred to as dialysis encephalopathy or dialysis dementia (85). This disorder is characterized by progressive speech disturbance, dementia, and convulsions. The brain tissues, muscle and bone of affected patients show markedly elevated aluminum content. It is generally fatal within six months, although some patients have had clinical improvement following chelation therapy (86,87). In general, the aluminum is thought to originate from either dialysis fluid containing excess aluminum or from excess oral intake (88). Nondialysis patients with this condition have been found among children with renal failure who were taking oral aluminum hydroxide preparations (89,90).

Other aluminum-related problems are seen in patients with chronic renal failure. Osteodystrophy occurs in patients who deposit large amounts of aluminum in their bones (91,92). These patients can develop spontaneous fractures and frequently will also have evidence of encephalopathy. One study has shown that the tap water of renal patients with the highest incidence of fractures and encephalopathy had concentrations of calcium and fluorine which were lower and concentrations of aluminum and magnesium which were higher than those in the water of patients without these complications (93).

Aluminum has also been considered to play a possible role in the etiology of Alzheimer's Disease. Aluminum salts can induce lesions in the nervous system of the cat and rabbit that are similar, but not identical, to those seen in the brains of Alzheimer's Disease patients (94,95). The studies of Crapper and coworkers have shown evidence of increased amounts of aluminum in the brains of individuals dying of Alzheimer's Disease when compared to nondemented controls (96). Attempts to reproduce this finding have produced varying results and remain controversial (97). Perl and coworkers have evaluated this question on a cellular level, using precise electron probe methods. Their data (98) indicate that aluminum accumulation is found in those neurons which demonstrate the presence of neurofibrillary tangles (one of the characteristic microscopic lesions of Alzheimer's Disease).

Similar findings have been reported in neurons containing neurofibrillary tangles in the brains of the Chamorro natives living on the island of Guam (99). The Chamorros have been extensively studied over the past 35 years in an effort to explain their remarkable tendency to develop neurofibrillary tangles associated with amyotrophic lateral sclerosis and Parkinsonism with dementia. Extensive data collected on Guam strongly suggests that the unusual tendency towards neurodegenerative disorders is related to local environmental factors and that aluminum accumulates in the brains of affected individuals.

Another recent study demonstrates that aluminum can affect the permeability of the blood brain barrier to small peptides, a change that may be related to the primary defect responsible for senile dementia (Alzheimer's Syndrome) (61).

The present state of knowledge indicates that aluminum in our environment as well as aluminum-containing products constitutes little, if any, risk of acute toxicity to the healthy population. However, those with chronic renal failure, particularly those undergoing renal dialysis, are especially vulnerable to the toxic effects of this element. Whether this risk significantly increases through the liberation of increased amounts of aluminum by the action of acid rain is a debatable question. There is certainly a great deal more aluminum within a single antacid tablet or slice of American cheese than is present in a gallon of stream water coming from an acid rain-washed region. The problem is that one cannot rely purely on a simple parts-per-million concentration of the element. We know very little about the various chemical species in which aluminum exists in nature and their potential bioavailability.

We have even fewer scientific data available with respect to the potential long-term effects of exposure to aluminum in our environment. Although aluminum has now been demonstrated within the damaged nerve cells associated with Alzheimer's Disease, it is still unclear if this phenomenon has etiologic significance. The data from Guam suggests that local environmental factors can play an important role, apparently acting through soil and water supply. Again, details of aluminum speciation on the island are lacking. Factors that allow aluminum to enter the nervous system of one individual and not another are not known. Field data indicate that one of the effects of acid rain is to increase the bioavailability of aluminum to flora and fauna. How high that concept extends up the biologic ladder is unknown. The possibility that it might extend to man is hypothetical, yet is certainly scientifically plausible.

Conclusions

Adverse human health effects, namely acute and chronic respiratory effects, can occur from the predeposition phase of the acid phenomenon due to inhalation of acidic particles and gases. State-of-the-art methodology to evaluate these effects is just now being applied to this question.

The major postdeposition effect of the acid rain phenomenon is to acidify water, increasing solubility and subsequent human exposure to mercury, lead, cadmium, and aluminum. Acidification increases the conversion of mercury to methylmercury, a highly toxic compound, which accumulates in fish, increasing the risk to toxicity in people who eat fish.

Increase in water and soil content of lead and cadmium increases human exposure to these metals which become additive to other sources presently under regulatory control. The potential adverse health effects of increased human exposure to aluminum is not known at the present time.

Deficiencies in the identification of the contribution of predeposition of air pollutants and postdeposition mobilization of toxic metals to the recognized potential health effects of the involved toxic substances are due to the fact that scientists have not addressed these specific questions.

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Appendix [illegible]

Conference on Health Effects of Acid Precipitation

November 15-16, 1984

National Institute of Environmental Health Sciences
South Campus Conference Room 101
Research Triangle Park, North Carolina

Thursday, November 15, 1984

8:30 a.m.	Comments - Objectives of Conference	Dr. Robert Goyer, NIEHS
8:45 a.m.	Overview - Acid precursor pollutants; emission, transport and deposition	Dr. Jack Durham, Env. Protection Agency
Session I -	Health Effects - Pre-depositional Phase of Acid Precipitation	Dr. Benjamin Ferris, Chairman
9:00 a.m.	Problems in the estimation of human exposure to components of acid precipitation precursors	Dr. Benjamin Ferris, Harvard Sch. Public Health
9:30 a.m.	Deposition of acid droplets in respiratory tract	Dr. Ted Martonen, Northrop Services, Inc.
10:00 a.m.	Effects of inhaled acids on respiratory tract defense systems	Dr. Richard Schlesinger, New York University
10:30 a.m.	Coffee Break	
10:45 a.m.	Effects of inhaled acids on lung mechanics	Dr. Mark Utell, University of Rochester
11:15 a.m.	Analysis of health effects resulting from population exposure to acid precipitation precursors	Dr. Haluk Ozkaynak, Harvard University
11:45 a.m.	Potential risks to human health from "acid fog"	Dr. Jack Hackney Univ. of S. California
12:15 p.m.	Lunch	
Session II -	Effects of Acid Precipitation on Mobilization, Transport and Speciation of Toxic Metals	Dr. William Sharpe, Pennsylvania State Univ.
1:15 p.m.	Corrosiveness of water and leaching of metals	Dr. William Sharpe, Pennsylvania State Univ.
1:45 p.m.	Effect of acid precipitation on water pH and metal bioavailability	Dr. Pamela Stokes, University of Toronto

Friday, November 16

ssion IV - Summarization of Sessions I, II, & III		Dr. Robert Goyer, Chairman
1:00 p.m.	Discussion of Session I - Estimates of exposure and human health effects to air pollutants related to acid rain	Dr. Morton Lippmann, New York University
2:00 p.m.	Discussion of Session II - Effect of acid rain on mobilization/transport/speciation of post-deposition of pollutants (toxic metals), including effects of corrosiveness, and leaching of metal content of soil/water/vegetation/food	Dr. John Wood, Gray Freshwater Biological Institute
3:00 p.m.	Discussion of Session III - Impact of effects of acid precipitation on toxicity of metals	Dr. Gunnar Nordberg, University of Umea, Sweden

Participants of the
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on November 15-16, 1984

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Appendix 3: NIEHS Research Program to Determine Health Effects of Acid Rain and Highlights of Accomplishments and Plans Addressing Research Needs to Determine Health Effects of Acid Rain

I. Research to Study Health Effects of Acidic Air Pollutants

The National Institute of Environmental Health Sciences (NIEHS) is currently sponsoring 18 research projects concerning effects of acidic air pollutants on human health. Studies cover a range of approaches including study of people in the ambient environment, people in chambers with controlled exposures, and a variety of animal models and *in vitro* studies. Overview and comment is provided for a number of these projects.

A. Studies Primarily Directed to Determine Health Effects of Acid Aerosols and Sulfur Compounds and Particulates

Particular attention should be given to the design, accomplishments, and research plans of one of these projects, the Harvard Six Cities Study, because it is an ongoing project that relates the health of selected human populations in cities with differing levels of air pollutants from fossil fuel combustion and constituents of acid rain.

Six cities were selected for study (Steubenville, Ohio; St. Louis, Missouri; Watertown, Massachusetts; Kingston/Harriman, Tennessee; Topeka, Kansas; and Portage, Wisconsin) because they represent a spectrum or gradient in severity of air pollution. Steubenville and St. Louis historically have air pollutant concentrations exceeding the National Primary Air Quality Standards, whereas Portage and Topeka are considerably below these standards. Also, the four cities with the highest pollutant levels (Steubenville, St. Louis, Kingston, and Watertown) are located in the "acid rain plume," an area extending from the midwestern portions of the United States to New England. Air pollution data are collected from outdoor and indoor environments and correlated with measures of pulmonary function and lung disease in selected adults and children. Populations from two other cities, Portage, Wisconsin, and Topeka, Kansas, are also being studied. These cities historically have lower levels of the air pollutants, sulfur dioxide (SO_2), total suspended particulates (TSP), and suspended sulfates (SS) than do the other four cities. An important aspect of the study is that it is "longitudinal" in design, that is, the same subjects, children and adults, are identified and followed periodically into the future. Parameters of growth of children can also be correlated with air pollutants.

The study is in its twelfth year and results to date show that frequency of cough in children is associated with the average of twenty-four hour mean concentrations of all three air pollutants during the year preceding their health examinations. Rates of bronchitis and a composite measure of lower respiratory illness are significantly associated with average particulate concentrations. In analyses restricted to lifetime residents, these outcomes were significantly associated with measures of lifetime mean TSP concentrations. Pulmonary function parameters were not associated either with pollutant concentrations during the year preceding the pulmonary function test or, for lifetime residents, with lifetime average concentrations. These results suggest that, for preadolescent children, exposure to moderately elevated concentrations of these pollutants may increase risk for bronchitis and other respiratory disorders, but have little or no effect on pulmonary function at least at the present time. The strong association between total sulfate concentrations and other measures of fine particles and symptoms of bronchitis suggest that exposure to these pollutants at the levels measured do have observable health effects.

One component of Harvard's Air Pollution Health Survey deals with development of an operational monitoring system for sulfate/sulfuric acid aerosol measurements. This was a research need emphasized in the NIEHS workshop report on acid rain. The system will be deployed in each of the six cities participating in the study. The monitoring is currently in effect in two of the six cities: Harriman, Tennessee, and Watertown, Massachusetts. This monitoring system when fully operational in the six cities will allow for apportionment of the total sulfates acidity to sulfuric acid and ammonium sulfate and provide information for studying human exposures to these two strong acids as present in acid rain. The combined data will provide a valuable measure of population exposures in conjunction with daily indices of acute upper and lower respiratory disease in each participating community.

B. New York University Studies

A second large study relating acid rain pollutants to human health is being conducted by the NIEHS Environmental Health Sciences Center at the Institute of Environmental Medicine, New York University. Investigators at this center have designed and developed a series of experiments in which rabbits as the animal model are exposed to ambient acids (related to acid rain) and the resultant effects on lung structure, respiratory mechanics, and specific pulmonary function are determined and correlated. Preliminary studies have demonstrated the effect of sulfuric acid aerosols on bronchial mucociliary functions to be similar in rabbits and humans. The rabbit animal model for the proposed studies was thus validated. Single short-term exposure to acid aerosols resulted in an accelerated tracheobronchial clearance upon low concentration exposure and retarded clearance after high concentration exposure as measured by clearance of radio-labeled latex particles. With these preliminary results, the investigators intend to conduct a thorough examination of lung histopathology, lung function as mucociliary clearance, and some measures of respiratory mechanics as a consequence of acid aerosol exposure of a variety of concentrations and durations of exposures. These studies involve both human and animal models.

Investigations with humans will be conducted in an environmental chamber providing controlled exposures to low-level acid pollutants in a double-blinded fashion. The subjects to be studied will be asthmatics and those with chronic bronchitis, pulmonary emphysema, or other chronic obstructive lung diseases. Patients with acute respiratory viral diseases will also be studied. Pollutants to be included will be sulfuric acid aerosols, ammonium sulfate aerosols, sodium chloride aerosols, and mixtures of sulfuric acid aerosols with nitrogen dioxide. Initial studies will use aerosols of 0.8 micrometers at concentrations of 50 to 75 micrograms per cubic meter and nitrogen dioxide at 0.20 ppm. Subsequent studies will involve increasing aerosols size up to ten micrometers to maximize bronchial deposition, or increasing relative humidity from thirty percent up to eighty percent. The experimental design will include exercise, carbachol challenge tests, and the measurement of endogenous ammonia in expired breath. Respiratory effects will be measured with pulmonary function tests that include airway resistance, and thoracic gas-volume flow-volume curves.

These studies should provide information toward establishing air quality standards that will protect populations particularly susceptible to low-level acidic pollutants.

The human studies will be complemented with studies in animals to investigate certain mechanistic aspects. Specifically, animals ~~will~~ have exposures similar to those of humans, but at somewhat higher concentrations. Endotracheal exposures will allow a differentiation between effects on conducting airways and alveolar defense systems. Measurements will include tracheobronchial permeability, histamine content, phagocytic activity of alveolar macrophages, alveolar epithelial permeability, and cellular components in both bronchial and lung lavage fluids. These animal studies are designed to elucidate mechanisms of action that could not be determined in humans.

C. Rancho Los Amigos Hospital Study, Downey, California

A study is underway by investigators in Southern California to determine short-term, health-related response in human volunteers breathing atmospheres containing "acid fog." The exposure atmospheres are designed to resemble Southern California fogs and eastern fogs of the type associated with past air pollution disasters. Healthy human volunteers as well as volunteers suffering with chronic respiratory disturbances will be evaluated during and after exposure to the controlled atmospheres.

D. Massachusetts Institute of Technology (MIT) Environmental Health Center Projects

At this NIEHS-supported Environmental Health Sciences Center, a number of studies on health effects of components of acid rain are underway. The effects of exposure to sulfuric acid mist upon the mucociliary clearance system is being examined in rabbit as an animal model. Clearance during the exposure period and for a pre-determined time afterward will be monitored by serial external measurements of an inhaled radioactively-tagged tracer aerosol. The study will provide information on the quantitative and temporal changes in mucociliary clearance and airway histology as these may relate to the pathogenesis of chronic bronchitis due to sulfuric acid exposures.

Particle induced x-ray emission is being employed in a selected human population to determine the effects on pulmonary function of exposure to low concentrations of gaseous SO_2 and fine aqueous aerosol droplets. Using these methods, it was demonstrated that one-half to three hour exposures to combinations of $SO_2 < 1$ ppm and aqueous aerosol droplets caused a significant increase in closing volume relative to vital capacity over that measured for non-exposure controls.

Prior studies in rats have shown that sulfur dioxide (SO_2) may potentiate the pulmonary carcinogenicity of polycyclic aromatic hydrocarbons (PAH), in particular benzo(a)pyrene (BP). Since man is exposed simultaneously to PAH and SO_2 in urban and polluted atmospheres and may, therefore, be at increased risk, a study is underway to investigate whether SO_2 alters the pulmonary metabolism of BP so as to increase exposure of lung tissues to toxic intermediates arising from BP.

Controlled coal combustion is being carried out in the laboratory to characterize the ultrafine combustion aerosols and sulfur dioxide formed and their effects on laboratory animals. Functional changes following exposure are evaluated by measurement of respiratory mechanics, and measurement of lung volumes. Pathological and biochemical parameters are also being determined. Information on the formation, interaction, and toxicological effects of the ultrafine aerosols and SO_2 are needed to design control strategies related to the combustion of fossil fuels.

E. Other Studies

In one study the effects of route of inhalation (oral versus oro-nasal) of sulfur dioxide and sulfuric acid on pulmonary function and the effect of pre-treatment with bronchodilator drugs on inhibition of SO_2-induced bronchoconstriction are being determined in either male or female allergic adolescents with or without asthma. The objectives of the project are to extend our knowledge of the effects of sulfur oxide air pollutants in susceptible individuals.

In another study, measurement of alterations of pulmonary mechanics in guinea pigs is used as a toxicological tool to evaluate response to irritants. Experiments are designed to furnish additional information in animal toxicology for the data base of air quality criteria for sulfur dioxides and particulates for ozone and for oxides of nitrogen.

Other studies show that mucociliary dysfunction occurs in airways following exposure to pollutant gases such as ozone and sulfur dioxide. The manifestations include loss of cilia, reduced ciliary beating, reduced mucus transport, and secretory tissue hyperplasia. This dysfunction may be exaggerated in allergic airways and may increase allergic airway disease. Studies to understand this phenomenon are being carried out using normal and allergic sheep.

II. Studies Primarily Directed to Effects of Acidic Air Pollutants Composed of Nitrogen Containing Compounds and Oxidizing Agents

A. Effects of Cells Lining Lung Surfaces

One project is studying the effects of the nitrogen oxide components of acid rain and ozone on the chemical composition of cells lining air sacs, the functional cells of the lungs where gases are exchanged with cells in blood.

In another study, it has been shown in preliminary experiments that there is an increase in tracheal and bronchoalveolar permeability to macromolecules following inhalation exposure of rats to ozone. The increased permeability appears to result, at least in part, from the perturbation of tight junctions between cells. It appears that the cytoskeleton is the likely target site for pollutant gases and that it plays a critical role in the modulation of tight junction permeability. These changes will be investigated more extensively in an animal model exposed to ozone and/or nitrogen dioxide.

B. Effects on Macrophages and Cellular Defense Mechanisms (Against Infectious Agents)

Several studies are underway to further investigate the suggestive evidence that a number of pollutant gases inhibit pulmonary macrophage phagocytosis. Using a combination of *in vivo* and *in vitro* experiments, the action of ozone and nitrogen dioxide on inhibition of phagocytosis is being determined.

The biochemical basis for the deleterious effects of oxidizing air pollutants with particular focus on cell membrane effects is underway and will utilize lung phagocytic cells. The effects of ozone and nitrogen dioxide on the production of superoxide anion radical on the fluidity of the plasma membrane and the electrochemical potential of the membrane will be determined.

C. Relationship of acid rain to emphysema studies are underway to determine the various parameters which influence the development of emphysema in hamsters exposed for long periods of time to NO_2. These include elastin degradation, impaired secretion of elastase by macrophages, and the effect of natural and synthetic protease inhibitors. The information should help to clarify the role of proteases in the neutrophil that are altered by nitrogen dioxide and related to the development of emphysema.

III. Research to Study Health Effects of Toxic Metals

Acid rain through the deposition of acidic materials on water and soil results in the mobilization, transport, and even chemical transformation of toxic metals. These consequences of acid rain, in turn, may increase human exposure to toxic metals by increasing soluble forms of metal in various media (food, water, air, etc.). In some instances, the metal may be transformed to a more toxic form, e.g., inorganic mercury to alkyl (methyl) mercury. A more detailed discussion of effects of acid rain on the potential toxicity of metals to humans is presented in summary papers of the NIEHS Conference on Health Effects of Acid Precipitation.

The NIEHS Extramural Program supports 52 projects concerned with some aspect of the biologic and human health effects of potentially toxic metals. Although some of these projects concern effects of more than one metal, the following comments highlight activities in progress in terms of only the four metals thought to be most affected by acid rain.

A. Research on Health Effects of Excess Exposure to Lead

The consequences of asymptomatic lead exposure in man and the development of rational approaches for their prevention and treatment are matters of continuing importance. Decrease in pH (acidification) increases solubility of lead compounds in water and amounts in living organisms and ultimately in man. Research supported by the NIEHS is concerned with a broad spectrum of scientific issues. These include the assessment of behavioral, reproductive, visual, neurological, gastrointestinal, and renal effects of lead exposure. In addition, research on the clinical assessment and therapy of lead exposure is being supported. Some of the research supported is described in the following paragraphs.

Dr. Robert Bowman at the University of Wisconsin in Madison, Wisconsin, is conducting studies to provide a description of the cognitive syndrome resulting from neonatal lead exposure and to develop test paradigms that are sensitive to the effects of low-lead exposure. This investigator has found that delayed spatial alternation is sensitive in detecting a persistent lead-induced cognitive dysfunction in six-year-old monkeys exposed to lead during their first year after birth. Studies are underway to determine the underlying mechanism of this effect.

Lead exposure can also have adverse effects on reproductive function. Dr. Rebecca Sokol at the University of California Medical Center in Torrance, California, has shown that testicular function and sperm production are affected at low levels of lead exposure. The hormonal mechanisms responsible for these effects have not been fully characterized, but their data suggest that the dominant mechanism of action of lead toxicity is at the level of the hypothalamic-pituitary axis. This investigator is determining the time course, dose dependency, and reversibility of reproductive abnormalities induced in male rats by daily exposure to lead acetate. The ultimate goal of this research is to delineate the mechanism(s) and site(s) of action of lead on the hypothalamic-pituitary-gonadal axis. Dr. Joseph Graziano at the Columbia University in New York, New York, is beginning a study to examine the relationship of chronic lead exposure to adverse pregnancy outcomes, infant development, and infertility. This study draws upon a unique community in Mitrovica, Yugoslavia, which is the site of a heavily polluting lead smelter.

The delineation of the adverse psychological and neurophysiological effects of childhood lead exposure remains a concern. Dr. Arthur Michaelson at the University of Cincinnati, Cincinnati, Ohio, is conducting studies at the cellular and neurochemical levels to assess the basis for the neuropsychological dysfunctions induced by lead. This investigator has proposed that a common mechanism underlies the central nervous system (CNS) neurotransmitter insult following neonatal exposure to lead. The hypothesis which he is testing is that inhibition by lead of the flux of calcium across the nerve terminal during neonatal CNS development will result in a persistent alteration in interneuronal calcium regulation that will be reflected in generalized alteration in transmitter release. This research will establish whether a generalized and persistent alteration in the neuronal calcium regulatory process is the basis of the CNS insult following neonatal lead exposure.

Dr. Carol Angle and associates at the University of Nebraska Medical Center in Omaha, Nebraska, are investigating the multifactorial interaction of lead and the red cell membrane. These investigators have shown that the maximum acceptable blood level (30 μg/dl) for children evokes hemolysis manifested by target cells with decreases in membrane fluidity, osmotic fragility, cell survival, and pyrimidine-5'-nucleotidase activity. The results from these studies may result in a more useful method for assessing low blood lead levels and provide new insight into the biologic effects of lead exposure of the general population as well as that of lead workers and young children.

Dr. Deborah Slechta at the University of Rochester in Rochester, New York, has proposed that juvenile and adult organisms may be more susceptible to lead neurotoxicity than commonly recognized. Recent data from her laboratory indicate that juvenile rats chronically exposed to lead in drinking water at a concentration of 50 ppm (blood lead 20-30 μg/dl) manifest distinctive behavioral phenomena. These appear as markedly elevated rates of responding in operant behavior testing. Studies are underway to determine the underlying mechanism(s) of this phenomenon.

B. Research on Health Effects of Excess Exposure to Cadmium

Cadmium is a widely dispersed toxic trace metal which is becoming an increasingly important environmental pollutant. Cadmium is not readily excreted by the kidney so that exposure results in progressively higher concentrations in body organs, especially liver and kidney. The NIEHS is supporting research to identify and determine the mechanisms of its biological effects, to assess the role of metallothionein in the biological response, and for the development of therapies. Some of the research in each area is described in the following paragraphs.

The mechanism of inhibition of biosignal transmission by cadmium is being investigated by Dr. Rama Sastry at the Vanderbilt University in Nashville, Tennessee. For these studies, two types of biosignal transmissions are being studied: phospholipid N-methylation (PMT) and acetylcholine (ACh) transmission. The PMT pathway is inhibited irreversibly by cadmium. In an effort to determine the mechanism of biosignal inhibition, several specific aims have been identified. The possible protective effects of zinc, cysteine, and metallothionein, the relationship between PMT inhibition and functional activity of tissues, and effects of cadmium on regenerating rat liver will be examined. The studies may help explain the muscle weakness and paralysis, depressed placental function, and general toxic effect on regenerating tissue by cadmium.

Immune functions are also affected by cadmium. Dr. Richard Winchurch and associates at the Johns Hopkins University in Baltimore, Maryland, are investigating which immune functions are altered and the mechanisms of their action. These studies include the investigation of the influence of cadmium on both cellular and humoral immune responses in adult and neonatal mice. In addition, the dose-response relationship for discrete immune functions and the metal and metallothionein content in various lymphoid and non-lymphoid tissue will be determined. Finally, the effects of cadmium on the response to endotoxin will be determined.

Dr. Ernest Foulkes of the University of Cincinnati in Cincinnati, Ohio, is examining the cadmium-induced nephrotoxicity. The nature of this effect, though well known, is not understood. This study focuses on the lesion leading to the aminoaciduria, i.e., the inhibition of amino acid resorption in the proximal tubule. The results so far show that this inhibition resembles a simpler system and may be referred to as uncompetitive inhibition. The significance of this concept has led to a new experimental approach which permits analysis of saturation and inhibition kinetics of amino acid transport without the complicating factors of long equilibrating infusions. The final outcome of the work should be a better understanding of how toxic metals are excreted by the kidney.

One of the consequences of cadmium exposure is the induction of the metallothioneins. These are low molecular weight, cysteine rich, heavy metal binding proteins. However, it is not clear whether the function of the protein is to protect the organism from toxic metal or to store necessary heavy metals for delivery at times and to organs where they are needed. Dr. Gustavo Maroni at the University of North Carolina at Chapel Hill, North Carolina, is investigating the role of metallothionein in protection against cadmium toxicity. This is investigated by obtaining mutants in Drosophila melanogaster, which are unable to produce normal metallothionein, and testing them for their sensitivity to cadmium. Dr. Robert Cousins at the Rutgers University in New Brunswick, New Jersey, is conducting studies to determine the mechanism of metallothionein induction. Polysomal and post-ribosomal poly(A)mRNA will be translated in a wheat germ system and newly synthesized metallothionein will be measured. The mRNA will be obtained from cadmium-fed and cadmium-injected rats and from isolated rat liver parenchymal cells in primary culture previously exposed to various treatments. In addition, the rate of metallothionein synthesis will be measured in rat kidney after injections and oral administration of cadmium.

Studies are underway to develop more efficacious therapies for cadmium toxicity.

C. Research on Biochemical Transformations and Health Effects of Mercury Compounds

One of the most prominent effects of acid rain is the effect of decreasing the pH of lakes and increasing the conversion of inorganic mercury to the more toxic methylmercury. Several studies on the health effects of methylmercury are concerned with neurotoxicity. One such study is directed toward the understanding of the sequential biochemical and early ultrastructural events induced by methylmercury in the cerebellum, in isolated cerebellar purkinge cells, and cell-free protein translation systems. Identification of the mercury-induced biochemical and ultrastructural lesions will provide means for determining sub-symptomatic neurotoxicity.

Another study will determine the effects of methylmercury on the growth and development of fetal brain. These studies are carried out in mice and human brain cells and pregnant mice exposed to mercury. The objectives of the study are to assess, in detail, the changes in development of fetal brain brought about by maternal intoxication of methylmercury.

Using intracellular microelectrode recording techniques and electron microscopy in conjunction with x-ray microprobe analysis, the mechanism of acute toxicity of methylmercury on presynaptic neuromuscular function is being studied in rats and mice. The results are expected to provide answers to questions regarding the mechanism of action of (methylmercury) on synapses, particularly its interactions with the voltage dependent Ca^{2+} channel and with nerve terminal Ca^{2+} buffering systems.

Another study is designed to determine molecular and cellular mechanisms by which congenital mercury exposure of rat fetuses results in smaller offspring and to congenitally expose monkey fetuses in a similar manner to determine the dosage levels and mechanisms producing similar changes in primates and to determine whether these changes alter growth, metabolism or the ontogeny of behavioral characteristics.

D. Research on Health Effects of Aluminum Compounds

Human exposure to aluminum through the environment is increasing due to solubilization in acidic water and possible chemical transformation. The hazard to man from this increased exposure is not understood. One study on aluminum employing rabbits exposed *in utero*, neonatally, during lactation, and as mature animals will assess the neurobehavioral toxicity of this metal at the various stages of development. The results of the study should further our understanding of the interaction between aluminum and some of the biological factors which seem to contribute to aluminum associated diseases such as dialysis encephalopathy and Alzheimer disease.

E. Other Studies Including Effects of Mixtures of Metals

A large multidisciplinary program project grant is focusing on four metals, mercury, lead, cadmium, and manganese, and encompasses investigations of the physical and chemical properties of metals and metal compounds that determine how they enter the body, how they are distributed, are metabolized, the mechanism controlling elimination from the body, and their capacity to impair the vital body processes. Special attention is paid to effects on major organ systems and to genetic factors.

The NA^+,K^+ATPase is an enzyme of the plasma membrane involved in the regulation of the internal ionic environment of most mammalian cells. Interactions of this enzyme with short-chain alkylmercury compounds, such as methylmercury, inhibit the NA^+K^+ dependent ATPase activity of the enzyme without inhibiting its partial reactions. The goal of this study is to understand the mechanism and elucidation of the mechanisms.

The effects of heavy metals on the immune system are the focus of two studies: one will determine the effects of metals on the structure and functions of murine lymphocytes to determine the short- and long-term effects of exposure to low levels of metals and will identify health hazards to certain populations and individuals; the second is aimed at an in-depth study of mercury in its various forms in relationship to the induction of autoimmune disease.

Other heavy metal studies include the role of methylation within mammalian tissues in producing toxic effects at the cellular and genetic levels to effect mutagenic manifestations, and the role of methylmercury in inhibition of DNA and RNA synthesis in cultured cells, and the interactions of methylmercury with selenium in various *in vitro* systems of nucleic acid synthesis.

Mr. CONTE. Dr. Rall, that report addresses the need for new research initiatives on acid rain that will better focus our knowledge of the devastation it causes.

From your statement, I got the impression that this money has been added to the FY 1987 budget. But, looking through the justifications, I did not see it mentioned anywhere.

Is that money included in the budget you have submitted to the Committee?

Dr. RALL. Not any more. We originally included it but with the various austerity aspects of the budgets, it disappeared.

Mr. CONTE. There is nothing in here for acid rain study?

Dr. RALL. There is no increase. There are the budget numbers I gave you. We will be able to maintain with very small changes.

Mr. CONTE. Are you carrying over——

Dr. RALL. We are carrying over about a $20 million program. We will not be able to increase it.

We had hoped to offer two Requests for Applications for grants on acid rain studies, and we will simply not be able to put those out.

ADDITIONAL FUNDS

Mr. CONTE. The new initiatives are estimated to cost about $3 million and required two positions to manage.

You are not asking for that money?

Dr. RALL. No, sir, we are not.

Mr. CONTE. Where should we put that money in?

Dr. RALL. That is primarily grant money in some of the centers and mostly for regular research.

Mr. CONTE. We may have to try to put it in the grant money.

My concern all along, Doctor, has been that, while the institute has conducted research into respiratory diseases related to acid pollutants, and has looked into the potential effects of human exposure to toxic chemicals, the effect was not focused enough to give us results on the real problems of acid rain.

I have been battling for years to get an acid rain bill, but people keep hiding behind the fallacy that the studies are not all in. Things have been looking up recently, and I am going to give it my best shot again.

The point is, Doctor, acid rain has costs in our environment and our livelihood, and it may be that it has costs in our lives and our health as well, and we need to find out the facts on this. Your institute certainly could help us.

Tell me what areas you will look at with this kind of new initiative? What gaps do we need to fill in to get a clearer picture of the health risk to humans from acid rain?

Dr. RALL. I would think that the report of Drew Lewis was very helpful. I found that surprisingly supportive of the sort of problems that we see.

Basically there are two areas that we think more research can be useful. I tend to feel, I think as you do, that we really are very close to knowing all we need about acid precipitation. But we are intrigued about the possible effects of aluminum, if it becomes solubilized and whether or not it can damage the central nervous system. We have discussed this before as an important area for new research.

Along with it, of course, the continuing problems of lead and the other heavy metals.

The interrelationship between the common air pollutants that in fact become acid precipitation is still not as well understood as it could be, the interrelationship between the sulfur dioxide, the zinc particles and moisture, nitrogen dioxide and so forth. It is very complicated atmospheric chemistry and we simply need to know a little bit more.

I think we are getting pretty close to where we can make more definitive statements about acid precipitation, and I hope we can do that in the next year or two.

Mr. CONTE. Well, that is good.

Are you getting all the help you need on studying these problems? The scientists are first-rate, and there is nobody getting in your way, is there?

Dr. RALL. No.

ADEQUACY OF BUDGET

Mr. CONTE. Doctor, it seems as though every day we are confronted with increasing uncertainties about the effects of various agents in our environment. It has put ever increasing demands on your institute to improve our knowledge of the chemical, physical, and biological makeup of our world.

In light of all that, and in the perspective of the institute's twentieth anniversary, do you feel comfortable with the size and scope of your operations under this budget request?

Dr. RALL. Well, I do not know a scientist or a scientist administrator who does not think that their institute needs more money, and I think you can take that as a given.

My honest feeling is that the 1986 budget hurts but we can live with it. We could probably, with significant pain, live with it for another year. But I think we are all very proud of the research machine we have put together and we really want to see it prosper rather than just bearly survive.

IMPLEMENTATION OF TASK FORCE III

Mr. CONTE. Your justifications say that the final implementation of the institute's Task Force III may result in some readjustments in emphasis under this budget.

Can you give us a little more insight on that? Which programs might need more attention and which ones less attention?

Dr. RALL. The main thrust of the Task Force III report is one that we really are already far along to implementing.

You have heard mostly other institute directors describe the new biology, the cloning of genes, the recognition of specific types of DNA with the relatively simple methodologies, the radioimmunoassays. These now provide a wonderful opportunity for environmental health science to move forward much more rapidly.

What it will do is not so much change the distribution between the program areas, but make progress faster with these new tools.

I discussed with the Chairman the problems of epidemiological studies. It is very difficult to know what people were exposed to 20 years ago. I mean what were you doing 20 years ago? What were you exposed to? This is almost impossible in a society such as ours which is mobile and ever changing.

We have reason to believe now that when some of these toxic agents interact with the body, they leave footprints which will stay for years and years and years. If we can identify those and say, by golly, there is evidence this person was exposed to this chemical sometime in the past, this should make our epidemiological studies very much more powerful. But it is not going to change what we are doing. Rather it is going to demand the use of much more complex and sophisticated technology to do a better job. I am very excited about it.

CHEMICAL TOXICITY STUDIES

Mr. CONTE. Your justifications also show that you will be conducting about 10 to 15 studies on chemical toxicity in FY 1987. That number may be in line with what you have been able to test historically, Doctor, but it seems like such an awful small number.

Do you feel that that is a sufficient number to be testing each year?

Dr. RALL. Historically, that is smaller than we have been in the past.

Three or four years ago, it was on the order of 35 or so.

Mr. CONTE. That is right.

Dr. RALL. I go back to what I said a few minutes ago, that we can live within our budget but it hurts. And we must live with it. I do not imply that I do not understand the necessity for fiscal austerity for everybody.

TESTING METHODS

Mr. CONTE. We cannot live with it very long or we will all be dead.

Are you getting better at developing testing methods that are less time consuming and less costly?

Dr. RALL. We hope so. We hope to report back next year the result of this large study of the feasibility of in vitro testing for quicker answers about toxicity I was discussing with the Chairman. As new methods are developed, everybody who develops a method thinks it is marvelous and writes it up in glowing terms suggesting that this is a wonderful method and will save money. But it is extremely important to really test and validate the method. Enthusiasm for the method does not always make it turn out right. Validating the scientific validity and comparing costs is a difficult problem and is what we have done and continue to do with many of these tests. And I worry that some of them will flunk, but hope that some will pass and those are the ones we will have to look at. And I will be back to you next year on it.

IMPROVEMENT OF TESTING SYSTEM

Mr. **Conte**. In your opinion, what might we do to improve the system to make sure that all the new chemicals entering the marketplace each year are safe?

Dr. **Rall**. Well, we really have done a remarkable job. This is also the tenth anniversary of the Toxic Substance Control Act which was the last sort of unfinished bit of environmental regulating legislation.

Now theoretically every new chemical is tested to see whether it is likely to pose unnecessary risks to human health if it is released into the environment. So, whereas some years ago, the system was incomplete, now it is complete. We think it is working, we think it is working better than it was a few years ago, and we take a little pride in the fact that it is one of our alumni, Dr. Jack Moore of the EPA, who is helping to make the system work better now than it had in the past.

I am optimistic in that sense.

SUSCEPTIBILITY TO CHEMICALS

Mr. **Conte**. One thing that occurs to me on the uncertainties of all these chemicals, the asbestos and the PCBs, the EDBs and all that, is that the risk from these chemicals may be genetically greater for some people than they are for other people. And I guess with all the institutes up here that we have testifying, we begin to look at these things in a grand scale.

But do you think it will soon be possible to assess an individual's genetic susceptibility to certain chemicals and pollutants, and to somehow then treat that problem?

Dr. **Rall**. Now we are getting very close to the ability to do that. It is going to pose a lot of problems when we do it.

If you find that somebody is susceptible to a particular kind of chemical but that, unfortunately, he is exposed to that in his workplace, it presents a terribly difficult risk management decision to make. Congress will eventually have to face that decision.

I think that science is moving along rapidly. We need some ethical and social considerations of how to handle this once environmental health sciences have defined persons at risk. I think we will find indeed that populations have a susceptible subset and a resistant subset, and we have to know how to handle this in our society.

Mr. **Conte**. Thank you, Mr. Chairman.

AVERAGE GRANT COST

Mr. **Natcher**. Dr. Rall, what was the cost of your average grant in 1985, and what average cost are you projecting for 1986 and 1987?

Dr. **Rall**. Let me divide those up a little bit. Let us deal first with the noncompeting.

Mr. **Natcher**. All right.

Dr. **Rall**. In 1985, $152,000, and that is history. We project that in 1986 it will be up to about $158,000 before sequestration, but $151,000 after sequestration. And in 1987, about $160,000 roughly.

If you talk about the new grants; in 1985 it was $128,000; after sequestration in 1986, $104,000, and the 1987 budget request we expect about $106,000.

Mr. **Natcher**. How do you feel about funding grants at less than the amount recommended by a study section?

Dr. **Rall**. I asked my Council that very question in January. Three-quarters of the people on the Council are those intimately involved in administrating grants. Their response was that a maximum of about a 10 percent reduction may be tolerated. Once it gets beyond a 10 percent reduction it begins to get too serious.

That is my sense also, and I have no evidence that downward negotiation of a few percent is not serious. On the other hand, it cannot go on year after year after year because much of that is postponement of important equipment and so forth. It seems to me it is sort of an emergency treatment, and some of it is okay, but if it lasts too long, it can be serious.

INDIRECT COST

Mr. **Natcher**. Doctor, I know you are familiar with the Administration's current proposal with respect to indirect cost.

Do you have any comments to make to us as to how you feel about this matter?

Dr. **Rall**. I really suspect that I cannot answer that intelligently. I do not know enough about administration of a university to know how seriously this will affect the universities. I would defer perhaps to Dr. Wyngaarden to discuss that. Because he has come recently out of a university.

Mr. **Natcher**. All right.

Now, Mr. Williams, if you will, please, we need a little clarification of yesterday's discussion. You are ready to clarify for us this morning. I can tell by looking at you. And in regard to indirect costs, the OMB's proposed change in Circular A-21, which is printed in the Federal Register for Wednesday, February 12th, provides that administrative costs shall be limited to 26 percent of direct costs as of April 1, 1987.

However, paragraph D of the proposed regulation says that implementation dates up to one year later are authorized.

Now, Mr. Williams, is it correct that the Department of Health and Human Services is proposing that the implementation date for the 20 percent be moved to an earlier date?

Mr. **Williams**. Let me say that the budget for the National Institutes of Health and for the Alcohol and Drug Abuse Administration assumes savings from implementation of this policy on a four-year basis in 1987. So that for the policy to be consistent with our budget request, the implementation date should be a year earlier—not a year earlier, but earlier than proposed in the February proposal. That is what I meant to say.

Now, I would emphasize that this is still a proposal. What is published in the Federal Register is a proposal, and the Office of Management and Budget has asked for public comments. And based on those comments, some final policy will be implemented, but it may not necessarily be the same as to what has been published.

Mr. **Natcher**. Mr. Williams, is it true that all other Federal agencies are proposing to defer the implementation date for a year? Is that your understanding?

Mr. **Williams**. I do not know what other people's specific plans are. I would not be surprised if that were true but I do not know.

Mr. **Natcher**. If you will, at this point in the record, give us a list of the institutions whose administrative cost rates exceed 26 percent as of today. If you would place that in the record for us, we would appreciate it.

[Information follows:]

MAJOR RESEARCH UNIVERSITIES WITH CURRENT ADMINISTRATIVE COST RATES EXCEEDING 26%*

1 ALBANY MED COLLEGE
2 BOSTON UNIV.
3 BROWN UNIV.
4 CARNEGIE-MELLON
5 COLORADO STATE UNIV.
6 COLUMBIA UNIV.
7 DARTMOUTH COLLEGE
8 DUKE UNIV.
9 EMORY UNIV.
10 GEORGE WASHINGTON UNIV.
11 GEORGIA INST. OF TECHNOLOGY
12 HARVARD MED SCH
13 HOWARD UNIV.
14 INDIANA UNIVERSITY
15 LEHIGH UNIV.
16 NEW MEXICO STATE UNIV.
17 NEW YORK UNIV. MED CENTER
18 OHIO STATE UNIVERSITY
19 RENSSELAER POLYTECH INST.
20 ROCKEFELLER UNIV.
21 RUTGERS UNIV.
22 STANFORD UNIV.
23 SUNY @ BUFFALO
24 SUNY @ STONY BROOK
25 SUNY DOWNSTATE MEDICAL CENTER
26 SYRACUSE UNIV.
27 TEMPLE UNIV.
28 THOMAS JEFFERSON UNIV.
29 TUFTS UNIV.
30 TULANE UNIVERSITY MED. SCHOOL
31 UNIV. OF ALASKA
32 UNIV. OF CALIFORNIA @ BERKELEY
33 UNIV. OF CALIFORNIA @ IRVINE
34 UNIV. OF CALIFORNIA @ LOS ANGELES
35 UNIV. OF CALIFORNIA @ SANTA BARBARA
36 UNIV. OF CHICAGO
37 UNIV. OF CONNECTICUT
38 UNIV. OF DAYTON
39 UNIV. OF DELAWARE
40 UNIV. OF DENVER
41 UNIV. OF FLORIDA
42 UNIV. OF ILLINOIS @ CHICAGO
43 UNIV. OF ILLINOIS @ URBANA
44 UNIV. OF KENTUCKY
45 UNIV. OF MASS. MED SCH @ WORCHESTER
46 UNIV. OF MED AND DENT OF NEW JERSEY
47 UNIV. OF MIAMI-MED. SCHOOL
48 UNIV. OF MICHIGAN
49 UNIV. OF NEW HAMPSHIRE
50 UNIV. OF NEW MEXICO-MED. SCHOOL
51 UNIV. OF NORTH CAROLINA @ CHAPEL HILL
52 UNIV. OF NOTRE DAME
53 UNIV. OF OKLAHOMA
54 UNIV. OF OREGON HSC
55 UNIV. OF PENNSYLVANIA
56 UNIV. OF PITTSBURGH
57 UNIV. OF SOUTHERN CALIFORNIA
58 UNIV. OF VERMONT & STATE AG. COLLEGE
59 UNIV. OF VIRGINIA
60 VANDERBILT UNIV.
61 VIRGINIA COMMONWEALTH UNIV.
62 VIRGINIA POLY. INST. AND STATE UNIV.
63 WASHINGTON STATE UNIV.
64 WASHINGTON UNIVERSITY
65 WAYNE STATE UNIVERSITY
66 YALE UNIV.
67 YESHIVA UNIV.

* THIS SCHEDULE COVERS MAJOR RESEARCH UNIVERSITES WHICH HAVE ADMINISTRATIVE COST RATES EXCEEDING 26% OF MODIFIED TOTAL DIRECT COST. "MAJOR RESEARCH UNIVERSITIES" ARE DEFINED AS THOSE THAT RECEIVE $6 MILLION OR MORE IN RESEARCH AND DEVELOPMENT FUNDS FROM ALL FEDERAL AGENCIES. THERE WERE 136 UNIVERSITIES IN THIS CATEGORY IN FY 1984 (THE LATEST YEAR GOVERNMENT-WIDE DATA ARE AVAILABLE); 67 HAVE CURRENT ADMINISTRATIVE COST RATES EXCEEDING 26%; 67 HAVE ADMINISTRATIVE COST RATES BELOW 26%; AND 2 HAVE RATES AT 26%. THESE 136 UNIVERSITIES ACCOUNT FOR OVER 90% OF THE TOTAL FEDERAL R&D FUNDS AWARDED TO ALL COLLEGES AND UNIVERSITES.

Mr. NATCHER. Thank you, Mr. Williams.

Mr. Conte, I yield to you.

Mr. CONTE. That was the series of questions you and I had yesterday, Mr. Williams. What you are saying is that HHS has worked it into their budget these savings for '87. In essence, what you are saying is that HHS is doing it this year—even though you do not know it, I am telling you, the other agencies have postponed implementation for a year.

Mr. WILLIAMS; That is correct. The budget assumes that we would implement it this year.

Mr. CONTE. That is right.

Mr. WILLIAMS. But as I emphasized before, this is still a proposal, and depending on whatever the final proposal is, it will be implemented government-wide.

Now, if there is——

Mr. CONTE. Not necessarily.

Mr. WILLIAMS. If there is one, let us say, for example, if the final rule that is published allows for only one implementation date and does not allow for implementation up to a year later, so then everybody would have to do it all at the same time.

Under the current proposal you are right, agencies would have an option to do it now or do it up to 12 months later. But that is still a proposal at the moment.

Mr. CONTE. And if that is the case, then who would make that decision? It has already been made because you have got it worked into your budget here.

Mr. WILLIAMS. Well, our budget does make some presumption about what the final policy would be, but that policy might change.

Mr. CONTE. And to override that, what we would have to do to is come up with that money that you have factored into your budget as a saving, and to enact some kind of a limitation provision to prevent you from implementing it for another year.

Mr. WILLIAMS. Yes, but it might be worthwhile waiting to see what the final policy is.

Mr. CONTE. By all means——

Mr. WILLIAMS. That would be done fairly soon in any case.

Mr. CONTE. What is the final policy?

Mr. WILLIAMS. Well, I think the comment period ends this week, so I would presume that a final decision on what the policy would be would come fairly soon thereafter.

Mr. CONTE. Okay. So we have some time.

Mr. WILLIAMS. While we are on the subject, let me clarify also another part of our discussion yesterday which I think was confusing.

Mr. CONTE. Okay.

Mr. WILLIAMS. And I have also had the opportunity to look into it.

Mr. Early asked whether there were institutions—the proposed policy this year would be to cap the administrative rate at 26 percent with a reduction next year down to 20 percent.

Mr. CONTE. Twenty percent.

Mr. WILLIAMS. The capping this year of 26 percent does have an effect on some institutions whose rates might be above that level. I was somewhat confused about that myself. Mr. Early pressed me on this issue yesterday, and I think his position was correct, that there are institutions this year who might be affected by that to the extent their rate is above that.

Mr. **Conte**. Yes. I think some were as high as 35 percent, I think I said yesterday.

Mr. **Williams**. It is useful to understand what the percentages mean. Twenty-six percent is for general administrative costs. That is only one of three or four elements to indirect cost.

The total indirect cost rate is about 48 percent.

Mr. **Conte** It is that high?

Mr. **Williams**. Which means that for every hundred thousand dollars that we put out for research, direct cost of research, we add on to that $48,000 for indirect cost, and of that $48,000, $26,000 is for general administrative costs; the other $22,000 is for other kinds of activities such as the library costs, operations.

Mr. **Conte**. Is that the way it works, or does it work this way here? If you give a grant to a medical school, for $100,000, $48,000 of that $100,000 is going to go for indirect costs.

Mr. **Williams**. The 26 percent rate is a percentage of the direct cost of the research. So if you are putting out $100,000 for research, then you add 26 percent on top of that for the administrative and direct costs, and another 22 percent for other aspects of that indirect cost rate.

So the overall indirect cost——

Mr. **Conte**. But that cost still comes out of this appropriation.

Mr. **Williams**. Oh, yes. It all comes out of——

Mr. **Conte**. And the appropriation for research includes money for overhead costs?

Mr. **Williams**. That is right.

Mr. **Conte**. And that means less for research.

Mr. **Williams**. Right, to the extent that money is given for indirect administrative costs, less is potentially available for direct research cost.

So if you look at that $48,000 in total, it is like $100,000 and an add-on of about $48,000; about 33 percent, roughly one-third of that total grant is going to indirect cost.

REPRODUCTIVE HEALTH

Mr. **Conte**. Sure.

Let me get back to my good friend here, Dr. Rall. With the rapid influx of women into the workplace over the last half century, growing attention has been placed on the risks that environmental hazards present to reproductive health. The problem may be equally as great for men as well.

What is your institute doing to help us better understand the nature and extent of the risks to the nation's reproductive health? Are you looking at this problem?

Dr. **Rall**. In our intramural program, we have one laboratory devoted to reproductive and developmental toxicology. It is headed by a scientist by the name of John McLachlan who has a very distinguished career. He was the first one who demonstrated that the DES-daughter problem with respect to vaginal cancer after DES administration to the mother could be perfectly replicated in experimental animals and can be studied.

He has gone on to show that many other such estrogens can pose problems and has very interesting insights into the mechanism of this.

So that laboratory animal level is exploring many problems of reproductive toxicology.

Our biometry and epidemiology group has begun a series of studies using now a new assay for human chorionic gonadotropin which allows the detection of pregnancy within a few days, much earlier than ever before by other methods. And he is looking at the effect of environmental agents on fertility, pregnancy rate and so forth. I think some of the work is very exciting. There is some preliminary evidence, for instance, that heavy smokers, women who are heavy smokers are somewhat less fertile than women who are not smokers. If their husbands are smokers, it does not make any difference. Preliminary, but very interesting.

We think this is a very important area, and we are pursuing it as vigorously as we can.

COUNCIL ON ENVIRONMENTAL QUALITY

Mr. Conte. About a month ago I received a copy of a 1984 annual report of the Council on Environmental Quality. The annual report, as I understand it, is circulated around different Federal agencies for more than a year before it hits OMB. Then, of course, it takes another year to reach the Congress.

Did you have any input on ~~this~~ report?

Dr. Rall. We generally have input on the health part of it. I do not specifically remember anything for this last report.

Mr. Conte. I can understand that because there is a grand total of one page directly devoted to environmental health out of a 711-page report.

Dr. Rall. That does not seem quite adequate to me.

LEAD

Mr. Conte. No, it does not. Here is the report, Mr. Chairman.

One of only two clear-cut environmental health issues they raise is the correlation between blood lead levels and lead in gasoline. In 1985, the report says the CDC lowered the allowable threshold for blood lead in children by five micrograms, and we suddenly saw a three-fold increase in the number of children needing treatment.

What can you tell us about the treatment used for children with high levels of blood lead? And how serious a problem is it in your view? What kind of things are going on at the institute to address this particular issue?

Dr. Rall. In my opening comments, I referred to the fact that we are learning increasingly about the relationship between blood lead and intellectual development of children in studies that we have supported. We do not have this research going on in-house.

They have demonstrated an increasingly strong effect of high blood levels on developmental problems in children. The results of this is the blood lead levels that are considered of concern have dropped from 40 or 50 micrograms per deciliter to 20 or 30. And this then primarily requires the children be removed from the environment which has the lead or the lead to be removed from the child environment. In cases of acute exposure and very high lead levels, medical treatment is necessary.

You can use chelating agents which remove the lead, but the best thing to do is to try to get the child away from the lead, feed him plenty of milk and calcium and so forth. That is probably the best thing to do.

But it is through findings of additional research that lets us more precisely say where the danger level is in chronic low-level exposure, and I think that is what you were describing.

DOCTORATE LEVEL EDUCATION

Mr. **Conte**. The other environmental health issue this great book raises acid deposition. Let me quote what they say: "Concerns may or may not be genuine." And if they are, "The next step is to assess the extent of the problem and its impact." I hope we are doing a lot more than that in that area.

Another report I received a few months ago was the 1985 report of the National Science Board, an eminent group chaired by Roland Schmitt, the senior vice president of R&D for General Electric Company. There are a number of noteworthy 1985 science indicators that I hope you will comment on for us.

I was interested, first of all, to note that the number of full-time graduate students in the field of environmental health increased 19.6 percent between 1973 and 1983. In the health sciences, there was an increase of 29.9 percent during that same period. With the exception of engineering and, of course, computer science, this marked the greatest jump in all the S&E fields.

Are we seeing, Doctor, an increase in the quantity, or more importantly, the quality of doctorate level education in the field of environmental health?

Dr. **Rall**. I think so. I am pleased to report. I would ask you to go back in history a little bit, and in 1976 this Committee was kind enough to supplement our research training budget. I think it was from about two-and-a-half million to three-and-a-half million dollars, and that supplement let us increase the training of environmental health scientists by about 30 or 40 percent beginning in 1976 on until now.

RESEARCH TRAINING

Mr. **Conte**. NIH as a whole, despite our best efforts on this Committee, has unfortunately represented the greatest decrease of all the S&E support sources during that 1975 to 1983 period. NIH support for full-time science and engineering graduate students has declined an average of 1.5 percent per year, while DoD support has increased an average of 3.9 percent, and foreign sources of support have increased a whopping 5.9 percent per year. Overall, your budget shows another decrease in your support for training in FY 1987. What does this trend mean for the future of environmental health science? And are we assuming that DoD, private industry or foreign sources will support research and training in this particular area?

Dr. **Rall**. This is the first year we have gone down. We have reduced the money available for research training, and we did that with great reluctance. But too many difficult decisions had to be made to do anything else. Up until this year, we have either increased or maintained training dollar levels.

Mr. **Conte**. How much more money will we need to bring it up to last year's level?

Dr. **Rall**. $350,000.

So we did not reduce it very much.

Mr. **Conte**. Well, that $350,000 could help quite a few students.

Dr. **Rall**. Yes.

Mr. **Conte**. The report also shows that in 1983 about 30 percent of the doctoral scientists and engineers employed by four-year colleges and universities were 40 years of age or over. Ten years ago that figure was 44 percent.

With declining Federal support for tbis work force, are we losing the youth and therefore the future of science in the United States?

Dr. **Rall**. I think we are, and all of us very concerned. We need to vigorously support research training to attract the best and the brightest to the biomedical sciences. In many ways, the future of the health of the country is dependent, among other factors, certainly, but on the quality and quantity of biomedical health. And I think we are all worried that as these budgets go down, as they really kind of have to now, we will not attract these very good students, and the consequences are not good.

Mr. **Conte**. We will see if we can help you, Doctor.

Thank you, Mr. Chairman.

Mr. **Natcher**. Mr. Hoyer

BURNING OF TOXIC WASTES

Mr. **Hoyer**. Thank you very much, Mr. Chairman.

Dr. Rall, I apologize for being late. I would like to ask just a few questions.

As you are probably aware, Doctor, there has been considerable discussion and disagreement over the burning of toxic wastes on the Atlantic Ocean off the coast of Maryland.

Have you been involved in this issue at all?

Dr. **Rall**. I am pleased to say we have not been involved in it. It is a very difficult issue.

Mr. **Hoyer**. Have you made any judgments at all? Has your shop been called upon for advice or expertise?

Dr. **Rall**. Let me separate the issues because there are two basic issues. One, the thing that seems to be the most worrisome is transporting large amounts of highly toxic chemicals to the place out in the ocean where you are going to burn it. That, I think, worries everybody.

No system is perfect. You can have everything set up beautifully, but accidents inevitably happen.

The technical issues about whether it is possible to effectively burn PCBs and get rid of all the toxic compounds in complex. As a non-expert I think it is possible. But again, we do not live in a perfect world, and one would hate to see a misfiring in the burning of a bunch of toxic chemicals, such that they were not destroyed, they were just volatilized.

So the issue, I think, is one of being able to really do it properly as opposed to the fact that technology is there, that if it works, it works.

REDUCTION IN RESEARCH CENTERS

Mr. HOYER. Well, I appreciate your comments. I understand you have not been intimately involved in the consideration, but I think you made some sound comments.

Last year, Doctor, you highlighted the excellent work being done in your research centers. At the same time, however, last year we noticed that there was a six percent cut below what you had in the previous year. It is six percent below the '86 full cost this year, as I understand it.

Last year, there were 18 centers, I believe, that were unfunded; is that correct?

Dr. RALL. There were 18 applications reviewed last year.

Mr. HOYER. First of all, let me ask you how has the sequestration affected the research centers?

Dr. RALL. They lost 4.3 percent like everybody else.

Mr. HOYER. I understand that because that was across the board.

Dr. RALL. Yes.

Mr. HOYER. What impact does that have on the ability to perform the tasks assigned?

Dr. RALL. It will simply make it more difficult. The centers are one area that we can go to for help in emerging problems. As they have to tighten their belt, they have less freedom to explore new and important areas.

Mr. HOYER. How many research centers will be funded in '87?

Dr. RALL. Fifteen; the same as last year.

Mr. HOYER. So there will not be any cutback?

Dr. RALL. No.

Mr. HOYER. It would be your perception then, if Gramm-Rudman was implemented—if we had sequestration again in October, that there would be an across the board cut again?

Dr. RALL. Yes.

Mr. HOYER. Okay. How many center applications will go unfunded this year in 1987, do you think? What is your projection?

Dr. RALL. I do not know. I will have to supply that for the record.

Mr. HOYER. And if you are going to supply that, if you could perhaps give us a listing of the ones that will go unfunded as well.

[Information follows:]

RESEARCH CENTER

The application review cycle for FY 1987 has just recently begun and we do not yet have complete information on the number of center grant applications that might be submitted. We do know, though, that there are currently four applications in the review process and all will be potentially eligible for funding. These applications are from the University of Connecticut, State University of New York, Stony Brook; University of Maryland; and the University of Wisconsin, Milwaukee.

LOW BIRTH WEIGHT

Mr. **Hoyer**. Doctor, can you now make a direct correlation between exposure to certain substances and low birth weight and birth defects? The environmental impact, in other words, on birth defects.

Dr. **Rall**. We can estimate the potential impact on birth defects from a great number of substances. The area that we are less certain of, but an area that seems of great importance, is the general toxic effect that many chemicals on the developmental process in utero, where you end up with a low birth weight with its associated problems, that we are working on and we do not have an answer yet.

One of our screening systems for reproductive and teratological effect is just to measure the weight of the newborn mouse and rat babies, and there seems to be a correlation between general toxicity and birth weight. That is one of the interesting areas, and we hope to know more in the next year or two.

Mr. **Hoyer**. Have you issued preliminary reports on that?

Dr. **Rall**. Yes.

QUALITY AND QUANTITY OF THE WATER SUPPLY

Mr. **Hoyer**. Last question, Doctor; all of us are very concerned about the future of the nation's water supply, obviously, and this is something that your shop, I know, has focused on. I am concerned about the contamination by chemical substances and acid rain. That may be a redundancy.

The water supply in the northern part of our nation appears to be in danger from acid rain, and the west continues to have inadequate supply to meet the needs of its growing population.

Generally, can you tell me how your shop views the future of our water supply in North America, its availability and its integrity?

Dr. **Rall**. Some of the great thinkers of the world, back in 1973 and 1974, when we were facing our first energy oil crisis pointed out that the problem in the 1980s and the 1990s and in the new century will be simply a shortage of fresh water. Well, it certainly did appear to some extent on the West Coast a few years ago.

So there is an issue of quantity that is a major problem.

In terms of the quality, though, the part we play in that is studying the toxicity of contaminants found in drinking water. And we have studies ongoing or completed on many of the common drinking water contaminants, but we are initiating a new series of studies which are very ambitious and very complex. Because you do not drink water with just one contaminant in it; it may have as many as ten or 15 or 20. And as toxicologists, we are not quite able to handle so-called combination toxicity. Or how do you handle the toxicity of ten contaminants at the same time?

So we have designed a series of tests where we have water with the 28 most common contaminants at the concentration they are found, and that will be fed to one group of animals, then ten to a hundred times the concentration fed to other groups of animals. These studies are just planned. They have not started yet, but it is really this looking at the combination toxicity that is going to help very much in assaying the safety of our drinking water.

As I discussed earlier, some studies on the solubility of aluminum and heavy metals are ongoing because that is one way we can get exposed to such agents, by acid precipitation, increasing solubility and ingestion by drinking water.

So we are working very diligently on those parts, and we keep in close contact with our colleagues in the EPA's office of drinking water.

Mr. HOYER. That was the question I was going to ask. Is there very close coordination between the efforts of your offices?

Dr. RALL. Yes.

Mr. HOYER Thank you very much.

Thank you, Mr. Chairman

Mr. NATCHER. Any further questions?

Mr. HOYER I have no further questions.

Mr. NATCHER. Dr. Rall, we want to thank you and your associates for appearing before our Committee at this time on behalf of your budget request for the Fiscal Year 1987. It has been a good hearing, Doctor, and we appreciate it.

Dr. RALL. Thank you very much.

[The following questions were submitted to be answered for the record:]

IMPACT OF GRANT REDUCTION

Mr. Early. With the original amount available for FY 86 and under the revised FY 86 proposal, NIEHS would be able to fund 111 new and competing research grants. Under the Administration's FY 87 proposal, NIEHS will fund only 105, or 6 fewer. What areas of research would be affected by this reduction?

Dr. Rall. Until all grant applications are received and peer reviewed, it is dificult to state which grants will or will not be funded. However, it is probable that research project grants focusing on the mechanisms of toxic response to xenobiotics such as cadmiums, chlorinated hydrocarbons, sulfinated compounds and nitrogen oxides and nitrosyls will not be awarded.

PAYLINE

Mr. Early. The FY 87 budget request would fund 105 new and competing grants, 6 fewer than the FY 86 level, pre or post-sequestration, and 3 fewer than FY 85. To what payline would you fund under the FY 86 revised request and under the FY 87 budget request?

Dr. Rall. The payline for FY 1986 is estimated to be 200 and the payline for FY 1987 is estimated to be 190.

Mr. Early. What was your payline in FY 85?

Dr. Rall. The payline for FY 1985 was 203.

PERCENTAGE OF GRANTS FUNDED

Mr. Early. What percentage of approved grants would be funded under the FY 86 revised and FY 87 budget requests?

Dr. Rall. The percentage of approved competing grants to be funded is estimated to be 30.6 in FY 1986 and 25.2 in 1987.

Mr. Early. How does this compare to your original FY 86 estimates and your FY 85 actuals?

Dr. Rall. The original FY 1986 estimate was 30.6 percent and the FY 1985 actual was 32.3 percent.

DOWNWARD NEGOTIATIONS

Mr. Early. The budget justification states that there will be downward negotiations of 6.5% and 8.8% in competing and non-competing grants, respectively. Will each grant be reduced by these amounts, or are these averages?

Dr. Rall. These are averages. Programmatic adjustments will be considered on an individual basis.

Mr. Early. Historically, non-competing research grants have been funded at close to the full commitment levels (99%). Why should these grants be funded at less than the approved levels after having been reviewed?

Dr. Rall. In keeping with the spirit of the Balanced Budget and Emergency Control Act of 1985, some difficult decisions had to be made. It was felt, not only in this Institute, but throughout NIH that the full protection of noncompeting awards at the expense of competing awards was unacceptable.

FUNDING OF RESEARCH CENTERS

Mr. Early. Although the same number of research centers (15) will be supported under the post-sequestration level as under the FY 86 enacted level, there will be a reduction of $662,000. How will this reduction impact the centers program?

Dr. Rall. This will result in a reduction of funds available for core or support activities for some of the research projects included in the centers research programs. Reductions will likely be reflected in decreased equipment purchases and other support needs that can be postponed.

Mr. Early. Will each center share evenly in this reduction?

Dr. Rall. The individual projects of each center will be reviewed and reductions negotiated in order to have the least negative impact.

Mr. Early. Will all centers be cut by the same amount?

Dr. Rall. Reductions will be negotiated for each center to minimize the negative impact.

Mr. Early. Will these reductions apply to both competing and non-competing centers?

Dr. Rall. Yes, the reduction will apply to each type of award.

Mr. Early. How were these amounts arrived at -- were these figures arrived at after careful and thoughtful review or did you have a set figure you had to work towards?

Dr. Rall. We were working within an overall framework but the reductions by mechanism of funding were arrived at after review of the scientific program needs in the context of the mission of NIEHS.

REDUCTION IN SIZE AND SCOPE OF CENTERS

Mr. Early. Doctor, will you summarize with some specificity, the effect the proposed reduction in size and scope of the centers program will have on NIEHS program plans--both immediate and long-range. What effects will these cuts have on the programs at the centers?

Dr. Rall. The immediate effects of the reduction will mean less vigorous support of research on new initiatives to utilize marine and freshwater models for the studies of the effects of environmental agents on human health, new initiatives related to the acid rain phenomenon, and new initiatives in molecular epidemiology. Naturally, a continued lack of support for the centers would eventually make it impossible to keep a critical mass of scientific talent together and apply it to complex scientific questions, which typify all environmental health research needs.

NEW INITIATIVES

Mr. Early. Will the FY 87 budget request enable NIEHS to undertake any new initiatives?

Dr. Rall. There are 67 new research project grants included in the budget request that will deal with such areas as air pollutants, industrial intermediates and by products, and metallic elements.

IMPACT ON RESEARCH

Mr. Early. Doctor, in the past, when you've had reductions in direct costs, what has been the effect -- are research teams disbanded; are projects that are postponed or temporarily scaled back resumed?

Dr. Rall. In the past, we have experienced reductions in grant direct costs only slightly above historical funding levels. These reductions were accomplished by not completely staffing up immediately, postponing equipment purchases, and so forth. Our National Advisory Council is of the opinion that reductions exceeding 10 percent could be disruptive.

USE OF ADDITIONAL FUNDS

Mr. Early. If an increase over the FY 87 request is provided, how would you use these additional funds?

Dr. Rall. Our first priority would be to restore the cuts negotiated in research project grants. Next we would bring our centers to their original level, and thirdly, resume a planned level of chemical testing under contract. Any funds above this would be used in acid rain research, oncogene studies, and methods development and validation.

DESCRIPTION OF NEW INITIATIVES

Mr. Early. Will any significant new research initiatives be lost or delayed by lack of funds in the FY 87 budget?

Dr. Rall. There are initiatives or opportunities that will be postponed.

Mr. Early. Please provide, for the record, a list of these along with a brief description and the funding requirements associated with each.

Dr. Rall. The following are examples of opportunities that will be pursued if funds are available:

- New grants focusing on the mechanisms of toxins response to xenobiotics such as cadmium, chlorinated hydrocarbons, sulfinated compounds and nitrogen oxides and nitrosyls - approximately $960,000;
- epidemiologic studies of the effect of acid rain on lung disease - approximately $1,000,000;
- the toxicology of aluminum on acid rain -- approximately $1,000,000;
- contracts on cloning and sequencing activated oncogenes and oncogene activation and molecular dosimetry in animal models which would produce information helpful in the estimation of human cancer risk -- approximately $500,000;
- development of an in vitro assay for chemically induced neoplastic transformation using oncogene-primed target -- approximately $260,000;
- mouse strain differences in hepatocarcinogenesis -- approximately $600,000;
- the response of centromeres to DNA damaging agents -- approximately $100,000.

ONGOING RESEARCH INITIATIVES

Mr. Early. Doctor, will any significant research initiatives currently underway be halted or seriously delayed due to FY 87 funding levels?

Dr. Rall. To some extent ongoing activities must be dalayed.

Mr. Early. To what extent will there be major reductions in the scope of ongoing or new initiatives because of the FY 87 funding levels? For the record, please provide a list of these along with a brief description and the amounts associated with each initiative.

Dr. Rall. The following ongoing activities will probably be affected in FY 1987:

- the number of new toxicologic characterization/carcinogenicity studies will be reduced from 15-20 studies to 10-15 studies -- approximately $4,000,000;
- delays will be experienced in implementing study design recommendations of the Ad Hoc Panel on Carcinogenesis Testing and Evaluation -- approximately $100,000;
- short term mutagenecity and fertility and reproductive studies will be reduced approximately 20-25 percent -- approximately $500,000;
- the Environmental Teratology Information Center, an information data base on teratogenic chemicals, will be eliminated -- approximately $400,000;
- support for the Environmental Mutagen Information Center, an information data base on mutagenic chemicals, will be reduced by approximately 25 percent -- approximately $100,000;
- funds for post-life audits will be reduced by approximately 25 percent, resulting in delays in efforts to have all current studies audited and funds for in-life audits will be reduced, resulting in a reduction of 35-40 percent in the number of units to laboratories by independent auditors -- approximately $500,000;
- support for several methods development and validation contracts will be reduced -- approximately $2,300,000.

RESEARCH AND DEVELOPMENT CONTRACT REDUCTION

Mr. Early. The FY 87 request and the revised FY 86 will support only 168 research and development contracts as compared to the FY 86 enacted level of 178 contracts. How will this reduction be achieved?

Dr. Rall. The reductions in research and development contracts affect both funding for methods development and validation and testing studies. In the area of methods development and validation, it has been necessary to cut back on the level of effort in this area by approximately 20-25%. New initiatives and opportunities in the methods development area are being deferred.

Mr. Early. What impact will it have on NIEHS current research activities and what about its future research initiatives?

Dr. Rall. In the toxicity and carcinogenicity testing program, the impact will be felt in FY 1987 and FY 1988. This is due to the fact that there is a certain amount of lag time from the date of awarding a contract to the time the actual testing begins. The lag time is necessary to procure and analyze the chemicals, assemble the animals, establish protocols, and so forth. We expect to begin approximately 40 studies in FY 1986. Only about 25 studies of the approximately 75 studies currently selected and approved can be initiated in FY 1987.

CLINICAL RESEARCH UNITS

Mr. Early. Doctor, will any clinical research units be supported under the FY 86 revised request or the FY 1987 request?

Dr. Rall. No clinical research units will be supported in FY 1986 or FY 1987.

Mr. Early. Do you still want to develop the clinical research units as part of the centers program?

Dr. Rall. Yes, we believe clinical research units will provide new direction.

Mr. Early. What has been the delay, fiscal constraints?

Dr. Rall. Because of budget uncertainties, requests for applications have not been solicited.

Mr. Early. If the funding was available, are you at the stage where you could implement clinical research initiatives? If so, please indicate what your first priority initiatives would be.

Dr. Rall. It would be difficult to identify and award clinical research units before late 1987 or early 1988. Priorities would include studies of respiratory diseases that might be caused by or influenced by acid rain and other pollutants. Other priorities would include clinical epidemiologic studies of chronic disease caused by environmental factors such as chronic renal disease and environmental factors that affect perinatal growth and development, such as chlorinated hydrocarbons and lead and other toxic metals.

Mr. Early. What would the estimated cost of these initiatives be?

Dr. Rall. Cost of these initiatives will be dependent on the funding mechanism. For most of these activities, specialized centers of research would be established in university departments and cost approximately one to two million dollars each per year.

PASSIVE SMOKING

Mr. Early. Are you planning to continue your research on passive smoking in FY 87 and if so, what are you planning?

Dr. Rall. Research on passive smoking will continue in FY 1987. Work will primarily focus on projects started in FY 1986, although new projects may be started as warranted by findings from current projects. Analysis of data from a prospective study of mortality from all causes and cancer incidence in persons who live with smokers will continue as will a study of risk factors for leukemia in which exposure to cigarette smoke during childhood is a major factor under investigation. In our earlier study, leukemia risk had been found to be increased for persons with one or more parents who smoked and to be greatest when both parents smoked.

Mr. Early. Would you briefly highlight your most recent findings concerning passiive smoking? What studies or research will be underway in FY 86?

Dr. Rall. Comparison of childhood smoke exposure histories provided by adults and by their parents showed that retrospective smoke exposure histories could be reliably obtained in interview studies. These findings will be published shortly in the American Journal of Epidemiology.

Preliminary analysis of the prospective study of persons living with smokers sugests that mortality from all causes, from ischemic heart disease, and from cancer is increased for persons under age 65 in 1963 who were living with smokers at that time. Preliminary analysis of data on specific cancer sites indicates that findings from our earlier study of cancer risk from passive smoking will be confirmed, at least for persons under age 45 at the beginning of the follow-up period.

A study of markers of possible genotoxic damage in smokers, passive smokers, and nonsmokers has found a small increase in numbers of sister chromatid exchanges in nonsmokers with measurable amounts of smoke byproducts -- passive smokers -- in their urine. These differences were seen using a nonstandard assay for sister chromatid exchanges and the mechanisms are not yet clearly defined. Further work will be done in this area.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

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NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

For carrying out sections 301, 311 and title IV of the Public Health Service Act with respect to environmental health sciences, [$197,686,000] *$187,995,000. (Department of Health and Human Services Appropriation Act, 1986.)*

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Amounts Available for Obligation [1]

	1985	1986	1987
Appropriation	$194,819,000	$197,686,000	$187,995,000
Enacted administrative reduction	—	-208,000	—
Sequester order	—	-8,492,000	—
Subtotal, adjusted appropriation	194,819,000	188,986,000	187,995,000
Comparative transfers for changes in central services financing mechanisms and formulas to:			
National Institute of General Medical Sciences	-49,000	—	—
Division of Research Resources	-714,000	—	—
Total, adjusted budget authority	194,056,000	188,986,000	187,995,000
Unobligated balance lapsing	-333,000	-99,000	—
Total obligations	193,723,000	188,887,000	187,995,000

[1] Excludes the following amounts for reimbursable activities carried out by this account: 1985 - $2,936,000; 1986 - $10,600,000; 1987 - $6,774,000.

National Institute of Environmental Health Sciences

Budget Mechanism
(Dollars in thousands)

Research grants	1986 1/ Appropriation No.	1986 1/ Appropriation Amount	1986 1/2/ Available after Sequestering No.	1986 1/2/ Available after Sequestering Amount	1986 1/2/ Revised No.	1986 1/2/ Revised Amount	1987 No.	1987 Amount
Research Projects:								
Noncompeting..........................	247	$39,173	247	$37,489	247	$37,489	229	$37,098
Administrative supplementals.......	(10)	528	(10)	505	(10)	505	(10)	514
Competing								
Renewal...........................	42	9,383	42	8,980	42	8,980	38	8,172
New................................	69	7,548	69	7,223	69	7,223	67	7,129
Subtotal, competing............	111	16,931	111	16,203	111	16,203	105	15,301
Subtotal, research projects..........	358	56,632	358	54,197	358	54,197	334	52,913
Research Centers........................	15	15,391	15	14,729	15	14,729	15	14,482
Other Research								
Research career programs...........	28	1,484	27	1,420	27	1,420	25	1,322
Minority biomed. res. support......	—	371	—	355	—	355	—	355
Other research related.............	6	443	6	404	6	404	6	420
Subtotal, other research..........	34	2,298	33	2,179	33	2,179	31	2,097
Total, Research Grants.........	407	74,321	406	71,105	406	71,105	380	69,492
Training								
Individual awards								
Noncompeting....................	18	344	18	344	18	344	21	420
Competing								
New............................	20	366	18	335	18	335	12	250
Subtotal, individ...........	38	710	36	679	36	679	33	670
Institutional awards								
Noncompeting....................	439	7,792	439	7,457	439	7,457	359	6,454
Competing								
Renewal........................	—	—	—	—	—	—	50	882
Subtotal, inst..............	439	7,792	439	7,457	439	7,457	409	7,336
Total, training....................	477	8,502	475	8,136	475	8,136	442	8,006

Research & Development Contracts....	178	54,443	168	52,102	168	52,102	168	52,045
Intramural Research.................		54,169		51,801	FTEs 579	51,801	FTEs 579	52,647
Research Management and Support.....		6,043		5,743	81	5,743	81	5,805
Total, NIEHS........................		197,478		188,887	660	188,887	660	187,995

1/ Reflects an enacted administrative reduction of $208,000.

2/ Reflects a consultant services (Section 515 of the Treasury-Postal Services Appropriation Act, 1985) withholding of $99,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

CROSSWALK - 1986 Appropriation 1/
(Dollars in thousands)

	MECHANISM								
	Research Grants			Training Programs					
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management and Support	Total
Characterization of environmental health hazards...............	$23,659		$951						$24,610
Biological response to environmental health hazards.........	25,132		799						25,931
Applied toxicological research and testing..	3,868		498			32,523			36,889
Biometry and risk estimation.............	3,973		50			1,920			5,943
Resource and manpower development...........		$15,391		$710	$7,792				23,893
Intramural research.....							$34,169		34,169
Research management and support...........								$6,043	6,043
Total........	56,632	15,391	2,298	710	7,792	34,443	34,169	6,043	197,478

1/ Reflects an enacted administrative reduction of $208,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

CROSSWALK - 1986 Available After Sequestering and 1986 Revised Request 1/2/

(Dollars in thousands)

	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management and Support	Total
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional				
Characterization of environmental health hazards................	$22,686		$896						$23,582
Biological response to environmental health hazards.........	24,102		735						24,837
Applied toxicological research and testing..	3,651		528			$50,182			54,361
Biometry and risk estimation.............	3,758		20			1,920			5,698
Resource and manpower development............		$14,729		$679	$7,457				22,865
Intramural research.....							$51,801		51,801
Research management and support............								$5,743	5,743
Total.........	54,197	14,729	2,179	679	7,457	52,102	51,801	5,743	188,887

1/ Reflects an enacted administrative reduction of $208,000.

2/ Reflects a consultant services (Section 95 of the Treasury-Postal Services Appropriation Act, 1985) withholding of $99,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

CROSSWALK - 1987 Congressional Justification

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management and Support	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional				
Characterization of environmental health hazards...............	$22,067		$909						$22,976
Biological response to environmental health hazards........	23,640		640						24,280
Applied toxicological research and testing..	3,539		528			$50,425			54,492
Biometry and risk estimation............	3,667		20			1,620			5,307
Resougce and manpower development...........		$14,482		$670	$7,336				22,488
Intramural research.....							$52,647		52,647
Research management and support...........								$5,805	5,805
Total.......	52,913	14,482	2,097	670	7,336	52,045	52,647	5,805	187,995

National Institute of Environmental Health Sciences

Summary of Changes

1986 Current estimated obligations	$188,887,000
1987 Estimated obligations	187,995,000
Net change	-892,000

	1986 Base Amount	Change from Base Amount
Increases:		
A. Built-in:		
1. Within grade increase	$24,524,000	+$218,000
2. Federal Employees Compensation Fund increase	98,000	+23,000
3. FTS rate increase	61,000	+14,000
4. Payment for centrally furnished services	1,609,000	+42,000
5. Increased cost of laboratory supplies, materials, and other expenses	30,059,000	+1,467,000
Subtotal		+1,764,000
B. Program:		
1. Research projects:		
a. Noncompeting continuations converting from competing status	37,994,000	+16,867,000
b. Competing (new and renewals)	16,203,000	+15,301,000
2. Research centers:		
a. Noncompeting continuations converting from competing status	11,974,000	+2,868,000
b. Competing (new and renewals)	2,755,000	+2,200,000
3. Other research grants:		
a. Noncompeting continuations converting from competing status	1,967,000	+221,000
b. Competing (new and renewals)	212,000	+106,000
4. Individual training awards:		
a. Noncompeting continuations converting from competing status	344,000	+349,000
b. Competing (new)	335,000	+250,000

Summary of Changes -- continued

	1986 Base Amount	Change from Base Amount
5. Institutional training awards:		
a. Noncompeting continuations converting from competing status.........	7,457,000	—
b. Competing (new and renewals)................	—	+882,000
6. Research and Development contracts:		
a. Continuations..............	51,682,000	+437,000
b. New	420,000	—
Subtotal, program..........		+39,481,000
Total, increases...............		+41,245,000
Decreases:		
A. Program:		
1. Research projects:		
a. Noncompeting completed or converting to competing status..................	37,994,000	-17,249,000
b. Competing completed or converting to non-competing status.........	16,203,000	-16,203,000
2. Research centers:		
a. Noncompeting completed or converting to competing status..................	11,974,000	-2,560,000
b. Competing completed or converting to non-competing status.........	2,755,000	-2,755,000
3. Other research grants:		
a. Noncompeting completed or converting to competing status....................	1,967,000	-197,000
b. Competing completed, or converted to noncompeting status....................	212,000	-212,000
4. Individual training awards:		
a. Noncompeting completed or converting to competing status..................	344,000	-273,000
b. Competing completed or converting to non-competing status.........	335,000	-335,000
5. Institutional training awards:		
a. Noncompeting completed or converting to competing status..................	7,457,000	-1,003,000

Summary of Changes -- continued

	1986 Base Amount	Change from Base Amount
6. Research and Development contracts:		
a. Continuations..............	51,682,000	-74,000
b. New..........................	420,000	-420,000
7. Intramural research............	51,801,000	-809,000
8. Research management and support......................	5,743,000	-47,000
Total, decreases.............		-42,137,000
Total, net change......................		-892,000

National Institute of Environmental Health Sciences

Budget Authority by Activity
(Dollars in thousands)

	1986 1/ Appropriation	1986 1/2/ Available after Sequestering	1986 1/2/ Revised		1987	
	Amount	Amount	FTE	Amount	FTE	Amount
Characterization of environmental health hazards.....	$24,610	$23,582		$23,582		$22,976
Biological response to environmental health hazards.....	25,931	24,837		24,837		24,280
Applied toxicological research and testing............	56,889	54,361		54,361		54,492
Biometry and risk estimation.........	5,943	5,698		5,698		5,307
Resource and manpower development..	23,893	22,865		22,865		22,488
Intramural research...........	54,169	51,801	579	51,801	579	52,647
Research management and support	6,043	5,743	81	5,743	81	5,805
Total obligations.....	197,478	188,887	660	188,887	660	187,995
Unobligated balance lapsing............	—	99		99		—
Total budget authority.........	197,478	188,986	660	188,986	660	187,995

1/ Reflects an enacted administrative reduction of $208,000.

2/ Reflects a consultant services (Section 515 of the Treasury-Postal Services Appropriation Act, 1985) withholding of $99,000.

National Institute of Environmental Health Sciences

Obligations by Object

	1985 Actual	1986 Estimate	1987 Estimate
Total number of full-time permanent positions.............	620	620	620
Total compensable workyears: Full-time equivalent employment..	735	725	725
Full-time equivalent of overtime and holiday hours.......	9	10	10
Average ES salary..................	$66,232	$66,232	$66,232
Average GS grade...................	9.14	9.14	9.14
Average GS salary	$28,224	$28,224	$28,224
Average salary grades established by Act of July 1, 1944 (42 USC 207)	$35,361	$35,361	$35,361
Average salary of ungraded positions	$23,206	$23,206	$23,206
Personnel compensation:			
Permanent positions	$14,904,000	$15,522,000	$15,677,000
Positions other than permanent..	4,610,000	4,785,000	4,833,000
Other personnel compensation....	444,000	461,000	466,000
Special personnel services	956,000	992,000	1,002,000
Subtotal, personnel comp...	20,914,000	21,760,000	21,978,000
Personnel benefits	2,660,000	2,764,000	2,816,000
Benefits for former personnel.....	94,000	96,000	100,000
Travel and transportation of persons	766,000	875,000	858,000
Transportation of things	159,000	160,000	157,000
Rent, communications and utilities.................	5,675,000	5,502,000	5,536,000
Printing and reproduction........	420,000	405,000	410,000

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	1985 Actual	1986 Estimate	1987 Estimate
Other services:			
Project contracts................	55,611,000	52,102,000	52,045,000
Centrally furnished services.....	2,132,000	1,609,000	1,651,000
Standard level user charges......	189,000	186,000	213,000
Other............................	12,544,000	11,330,000	12,756,000
Supplies and materials............	7,083,000	6,619,000	6,306,000
Equipment.........................	6,926,000	6,213,000	5,646,000
Lands and structures..............	25,000	25,000	25,000
Grants, subsidies & contributions..	78,523,000	79,241,000	77,498,000
Insurance claims and indemnities...	2,000	---	
Total obligations by object.	193,723,000	188,887,000	187,995,000

National Institute of Environmental Health Sciences

Significant Item in House Appropriations Committee Report

Item	Action Taken or to be Taken
1986 House Report	
Acid Rain	
1. "The Committee understands that a small amount of the funds added to the health science centers program in fiscal year 1985 may be used to begin to expand and initiate original research on the health effects of acid rain on humans, as the Committee requested in last year's report. The Committee is concerned with addressing this problem and therefore requests the Institute to develop a comprehensive plan for studying the human health effects of acid rain. This plan should be submitted to the Committee prior to hearings on the fiscal year 1987 budget, and should include a detailed outline of the Institute's programmatic, staffing, research and funding requirements to properly address this problem of growing national and international concern." (House Report No. 99-289, p. 70)	1. A report has been prepared and will be submitted to the Committee prior to the FY 1987 hearings.

NATIONAL INSTITUTES OF HEALTH
National Institute of Environmental Health Sciences

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1986 Amt. Authorized	1986 Estimate	1987 Amt. Authorized	1987 Budget Request
Research and Investigation.........	Section 301	42§241	Indefinite	$180,751,000	Indefinite	$187,995,000
National Institute of Environmental Health Sciences..............	Section 463	42§285l	Indefinite		Indefinite	
National Research Service Awards.........	Section 489	42§288	$260,000,000 1/	8,136,000	1/	
Total Budget Authority				188,887,000		187,995,000

1/ This training authority is shared with other research training programs of the National Institutes of Health, Health Resources and Services Administration, and the Alcohol, Drug Abuse, and Mental Health Administration.

National Institute of Environmental Health Sciences

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1978	$58,812,000	$64,241,000	$58,641,000	$64,241,000
1979	69,247,000	73,227,000	70,000,000	73,080,000
1980	79,406,000	83.912,000	83,912,000	83,893,000
1981	92,066,000	93,814,000	93,269,000	93,491,000
1982	96,851,000 2/	111,256,000	111,870,000	106,270,000
1983	157,448,000 3/	162,695,000	166,040,000	164,863,000
1984	165,884,000	173,627,000 4/	172,374,000 4/	179,802,000
1985	183,755,000	189,437,000 5/	191,908,000	194,056,000
Proposed Rescission	-542,000			
1986	183,679,000	188,319,000 6/	198,319,000	197,478,000
Sequester	-8,492,000			
1987	187,995,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations

2/ Reflects the September amendment; the original request was $110,058,000.

3/ Includes $48,165,000 to support the Bioassay Program transferred from the National Cancer Institute.

4/ Excludes $5,319,000 in NRSA training programs not considered.

5/ Excludes $5,922,000 in NRSA training programs not considered.

6/ Excludes $8,502,000 in NRSA training programs not considered

National Institute of Environmental Health Sciences

Justification
(Dollars in thousands)

	1986 1/ Appropriation	1986 1/2/ Available After Sequestration	1986 1/2/ Revised	1987
Characterization of environmental health hazards.....	$24,610,000	$23,582,000	$23,582,000	$22,976,000
Biological response to environmental health hazards.....	25,931,000	24,837,000	24,837,000	24,280,000
Applied toxicological research and testing............	56,889,000	54,361,000	54,361,000	54,492,000
Biometry and risk estimation....	5,943,000	5,698,000	5,698,000	5,307,000
Resource and manpower development........	23,893,000	22,865,000	22,865,000	22,488,000
Intramural research...........	54,169,000	51,801,000	51,801,000	52,647,000
Research management and support........	6,043,000	5,743,000	5,743,000	5,805,000
Total..............	197,379,000	188,887,000	188,887,000	187,995,000

1/ Reflects an enacted administrative reduction of $208,000.

2/ Reflects a consultant services (Section 515 of the Treasury-Postal Services Administration Act, 1985) withholding of $99,000.

GENERAL STATEMENT

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency conducting research on the effects of chemical, physical and biological environmental agents on human health.

The goal of NIEHS is to provide the scientific information base, advanced scientific methodology, and trained scientific manpower to reach an understanding of the impact of environmental factors on human health. NIEHS pursues its mission by supporting basic and applied research on the consequences of the exposure of man and other biological systems to potentially toxic or harmful agents in the environment.

Research of interest encompasses studies that relate to the biological effects of environmental chemicals and physical factors including such agents as hazardous gases, suspended particles, aerosols, industrial byproducts and intermediates, heavy metals, trace elements, food additives, adulterants and pesticides. Physical factors include noise, light, heat, microwaves, and other forms of non-ionizing radiation.

In support of research the NIEHS attempts to learn (1) the causal associations between human disease and hazardous chemical, physical and biological environmental factors; (2) the health effects of chemical, biological and physical environmental factors; (3) the processes by which environmental agents affect biological systems which result in human diseases and disorders; (4) the pharmacological principles that govern the site and severity of damage by environmental agents; (5) the details and time sequence of molecular, structural and functional changes resulting from exposure to environmental agents; (6) what chemicals are capable of altering the genetic makeup of man, reducing reproductive capacity, or damaging the embryo or fetus at any stage of differentiation and development; (7) the methods for development of reliable test systems for determining which agents are mutagens, teratogens, carcinogens or otherwise toxic; (8) the molecular and cellular mechanisms of mutagenesis, teratogenesis and organ toxicity; and (9) what aquatic or other forms are useful as models for environmental health studies.

As a research organization, NIEHS seeks to provide the essential knowledge base on the impact of environmental factors on human health which in turn aids those responsible for devising and instituting control or therapeutic measures. The information developed is therefore made available to regulatory agencies, other government agencies, the medical community, industry, and the general public for subsequent action. Accordingly, NIEHS research results form the primary basis for preventive programs for environmentally-related diseases and for other action by regulatory agencies.

In order to meet these ever-increasing demands the Institute supports a broad spectrum of research ranging from basic studies at the cellular and subcellular level to more applied programs aimed at detecting the toxic effects of various agents. This research is carried out at the Institute in its own laboratories and through grants and contracts at various universities, research centers and commercial facilities. Each of the three major research program areas, the Intramural Research Program (IRP), the Toxicology Research and Testing Program (TRTP), and the Biometry and Risk Assessment Program (BRAP), are assisted by advisory boards composed of scientists from outside NIEHS. These boards and the National Advisory Environmental Health Sciences Council aid the Director, NIEHS, in providing direction and oversight to the Institute's efforts. The peer review mechanisms are designed to assure that the research carried out in-house and supported through grants and contracts is of the highest quality.

It is clear that more and more chemicals and other potential toxins are being introduced or identified in our environment; as a result the task of studying each of these becomes increasingly difficult given finite resources. Much of the Institute's efforts are therefore directed toward studies of the basic mechanisms of action by which these agents adversely affect human health and at ways of predicting harmful effects by studying common characteristics of known toxins. If we can further understand what specific characteristics or mechanisms are dangerous we may be able to design new chemicals without those components or develop other blocking or neutralizing agents.

OVERALL BUDGET POLICY

The 1987 budget request for the NIEHS is $187,995,000, or $892,000 less than the 1986 revised level. The 1986 revised level contains a reduction from the original appropriation of $8,492,000 required by the Balanced Budget and Emergency Deficit Control Act of 1985, an enacted administrative reduction of $208,000, and a consultant services witholding of $99,000 required by Section 515 of the Treasury-Postal Services Appropriation Act of 1985.

These levels will be achieved by limiting indirect cost and by negotiating direct costs downward. The request will support 105 competing project grants at an average cost of $145,700. This represents a 2 percent increase in direct costs over 1986 and a 6.5 percent reduction from full recommended levels. Historically, these reductions have averaged 3 to 4 percent. The request will support 229 noncompeting project grants at an average cost of $162,000. This represents a 9.9 percent increase in direct costs over 1986 and an 8.8 percent reduction from full commitment levels. Historically, these reductions have averaged 1 percent.

In 1987, 10 Environmental Health Sciences (EHS) centers and 5 Marine and Freshwater Biomedical Sciences (MFBS) centers will be supported at a level of $14,482,000, compared to the same number of centers for $14,729,000 in 1986. This represents a 4.3 percent decrease in direct costs from 1986 and a 9.6 percent reduction from full cost levels.

All other research grant mechanisms will be supported at approximately the 1986 level.

An estimated 442 research trainees, 33 fewer than 1986, will be supported, contributing to the support of approximately 9,200 trainees NIH-wide. No stipend increase is being requested.

The request also includes $52,045,000 for research and development contracts that primarily support studies which characterize chemical toxicity and improve current test methods. The request is $57,000 less than 1986.

Intramural research and research management and support will be funded at slightly increased levels over 1986 of $846,000 and $62,000 respectively. This will necessitate program adjustments to offset mandatory increases of $1,764,000. The impact on direct laboratory research will be minimized to the extent possible.

As in previous years, the Institute will continue to utilize the majority of available funds to support grants and contracts with universities and other research organizations. The percentage of funds going into grant supported activities has risen steadily over the last several years and now stands at approximately forty percent. This figure is lower than the NIH average, reflecting the large contract effort supporting the National Toxicology Program.

The Institute continues to review this issue of balance among the various activities and mechanisms that are utilized to support its mission, and feels that the current mix is appropriate. Full implementation of Task Force III, the Institute's 1984 planning effort, may result in some readjustment, but no major changes are anticipated. The Institute anticipates increasing demand on the Toxicology Research and Testing Program to study more chemicals but this will have to be tempered by the need for more basic studies which may prove to be more beneficial in the long term. The Institute has assembled a cadre of outstanding scientists, who are supported with the latest necessary bio-technological innovations. This national resource was developed over many years and we are just now beginning to realize the maximum return on that investment. We will refine and focus our emphasis on those areas offering us the greatest promise, and encourage others to fill in the gaps. The Institute will also continue its cooperation with other federal agencies to ensure that national priorities are addressed while unnecessary duplication is avoided.

Program Accomplishments

The final report of the Ad Hoc Panel on Chemical Carcinogenesis and Testing Evaluation has been submitted to the NTP. The Panel, composed of distinguished representatives from industry, academia, and public interest groups, reviewed the basic biology and chemistry of chemical carcinogenesis and recommended to the NTP methods for use in the detection and evaluation of chemical carcinogens. The recommendations of the Panel have been reviewed and, for the most part implemented by the NTP.

For FY 1985, technical reports of 19 chemical toxicity studies were peer reviewed by the NTP Board of Scientific Counselors. Eleven chemicals showed evidence of carcinogenicity in rodents, 2 chemicals showed equivocal evidence of carcinogenicity in rodents and 6 chemicals showed no evidence of carcinogenicity in rodents.

In a 24 month rat carcinogenicity study of furan, an important chemical used as a solvent and in various manufacturing processes for the production of resins, proliferative lesions suspected as bile duct tumors of the liver were observed. Scientists were unable to determine whether this lesion, which is similar to that associated with the administration of polybrominated biphenyls (PBBs), was actually cancer or not. In an attempt to define the biologic potential of this lesion, recipient rats were innoculated subcutaneously and serial transplants were followed for eight generations. Tumor cholangiocarcinomas, or cancer of the bile duct, grew rapidly at the transplant site and spread to reginal lymph nodes, lung, and liver, confirming the malignant nature of these lesions. Therefore, if such tumors occur as a result of exposure to other chemicals, the carcinogenic potential of those chemicals will be more apparent.

Scientists know that opiates and opioid peptides exert major effects on behavior in humans and appear to be involved in experimentally-induced seizures. In a recent study, it was shown that chronic treatment with anti-psychotic drugs (haloperidol, for example) or repeated electroconvulsive shock increases the turnover and gene expression of opiate peptides in certain brain regions of the rat. Such findings have led to a new concept which suggests that gene expression is an important, if not essential, component in the behavioral consequences of psycho-active drugs and shock-treatment.

Nuclear Magnetic Resonance (NMR) is a relatively new, non-invasive tool for measuring the quantities and types of certain chemicals in cells, tissue, and whole animals. A new technique has been devised at the Institute for measuring minute quantities of calcium in cells using fluorine-containing structures that selectively interact with calcium ions. This new procedure now permits evaluation of the actions of hormones, toxic agents, and other factors on the concentrations of calcium ions under a variety of conditions and is a powerful adjunct to numerous studies that require knowledge of levels of calcium ions.

NIEHS jointly sponsored a conference with industry (November 18-21, 1985) on Managing the Conduct and Data Quality of Toxicology Studies. The conference, one of the largest ever convened by the Institute, drew over 600 participants from academia, industry, and government. It provided a unique opportunity for participants to exchange current practices, concepts, and new ideas for managing the quality of toxicology studies which have a regulatory impact at both national and international levels. These conference proceedings will be published during FY 1986.

Data collection for a four-center case-control study of risk factors for chronic renal failure has just been completed, and the data are now ready for analysis. Records for over four thousand hospital patients with renal disease were screened for new cases. 709 cases were eventually selected for interview, and 709 controls were chosen from social security listings and random telephone screening. Cases and controls have been interviewed regarding exposure to lead, cadmium, solvents, analgesic drugs and other environmental and occupational exposures of interest.

Studies of DNA adducts in human placental tissue have provided the first clear demonstration of DNA adducts in humans associated with cigarette smoking. The major adducts being formed by cigarette smoking *in vivo* do not seem to be caused by the polycyclic aromatic hydrocarbons or amines usually thought to be the most dangerous components of cigarette smoke. This work may ultimately lead to the identification of specific cigarette smoke components (as well as other environmental exposures) that damage human DNA.

Scientists in the Laboratory of Biochemical Risk Analysis, the Epidemiology Branch and the Laboratory of Pharmacology have demonstrated that placentas obtained from women in Taiwan who were accidentally exposed to rice oil contaminated with polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs) had dramatically elevated concentrations of a specific enzyme system (one isozyme of cytochrome P-450) although analyses were conducted four years after the exposure had occurred. Clinical symptomology characteristic of exposure to toxic halogenated aromatics was present in many of the newborns as well as the mothers. Ongoing studies are evaluating the role of dioxin receptor in individual variation in responsiveness to PCBs as well as the polychlorinated dibenzofurans. Concentrations of PCB and PCDF congeners in placenta and blood have been measured. These findings will permit the NIEHS to study mechanisms responsible for individual variation in responsiveness to PCBs and related compounds present in the rice oil which may lead to a rational process for identifying groups at risk to the toxic effects of compounds such as PCBs and dioxins.

A test has been developed to determine human exposure to a class of environmental carcinogens. This test gives information for the first time on actual long-term exposure of individuals to aromatic amines.

In a study on gamma rays and ultraviolet light which can produce damage in the DNA of mammalian cells, a mutant of mammalian cells hypersensitive to gamma radiation has been isolated for the first time.

National Institute of Environmental Health Sciences

Characterization of Environmental Health Hazards

1987 Authorization: Indefinite

Budget Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$24,610,000	$ 23,582,000	$23,582,000	$22,976,000	$-606,000

Purpose and Method of Operation

This program seeks to identify hazardous biological, chemical and physical factors and to establish the risk, if any, of exposure to these factors in various life situations primarily through the mechanism of research project grants. Understanding the relationship between exposure and resulting disease or biological injury is necessary to develop strategies for preventing human disease or injury from exposure to toxic environmental agents.

Within this program, emphasis has been and will continue to be placed on the development of reliable test methods, determination of the rates at which and routes by which environmental agents enter the body, and the metabolism and fate of toxicants. In pursuing program goals, a broad spectrum of substances are studied. These include industrial intermediates and byproducts; air pollutants such as ozone, sulfur and nitrogen oxides, and particulates; substances in chemical waste dumps; agricultural chemicals; and metallic elements such as arsenic, cadmium, mercury, lead, nickel, selenium, zinc and others. Physical factors with potential adverse health effects are also of interest. These include infrared, electromagnetic and microwave radiation, lasers, noise and ultrasound.

Rationale for the Budget Request

The 1987 budget request for this activity is $22,976,000, a decrease of $606,000 from the 1986 revised estimate. The decrease is related to program adjustments and indirect cost rate savings detailed in the General Statement. The requested level will fund 148 continuation and competing research project grants, 7 research career awards, and 3 other research grants.

Progress has been made in a number of important areas within this program. During the course of research on toxic chemicals in the environment, new sensitive diagnostic procedures to detect early effects and help in prevention of disease have been developed, for example a test has been developed that should serve as an early warning for exposure to mercury.

Research continues on an animal model that has been developed to characterize the respiratory allergenic potency of chemicals. This model will be important for characterization of industrial chemicals which cause allergic problems in humans. Serological investigations using these techniques were employed following the methyl isocyanate exposure incident.

Studies continue to assess the health effects of coal combustion-generated aerosols and their interaction with sulfur dioxide. Repeated exposure of laboratory animals to ultrafine aerosols of zinc oxide can produce persistent pulmonary changes.

The role of metals in urban atmosphere as a contributing cause of lung disease associated with air pollution is being investigated. The relationship between the clearance mechanism of the lung for metals and the exposure dosage may provide information as to threshold values.

Metallothionine may play an important role in the toxicity of the metal cadmium. One study has shown that the resistance of newborn rats to cadmium toxicity is due to large amounts of metallothionine in the liver, and that tolerance to cadmium is due to pre-synthesized metallothionine and not an increased capacity to synthesize this protein.

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987
Res. proj. grants				
Number	164	161	161	148
Amount	$23,659,000	$22,686,000	$22,686,000	$22,067,000
Other res. grants				
Number	11	11	11	10
Amount	951,000	896,000	896,000	909,000
TOTAL	24,610,000	23,582,000	23,582,000	22,976,000

National Institute of Environmental Health Sciences

Biological Response to Environmental Health Hazards

1987 Authorization: Indefinite

Budget Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$25,931,000	$24,837,000	$24,837,000	$24,280,000	-$557,000

Purpose and Method of Operation

This program is designed to develop a better understanding of the mechanisms of injury and disease caused by environmental factors, primarily through support of research project grants. Problem areas dealt with include, but are not limited to, neurological and behavioral disorders, respiratory disease, cardiovascular disease, biochemical and endocrine disturbances, kidney dysfunction, carcinogenesis, mutagenesis, reproductive disorders and birth defects.

Research focuses on perturbations by chemical and physical agents at the molecular, cellular, tissue and organ levels. This is a broad area of inquiry that integrates the traditional disciplines of anatomy, physiology, cell biology, endocrinology, genetics, biochemistry, and reproduction. By developing and applying knowledge of the effects of environmental agents on human metabolism, endocrine, immune, and other biological functions, disease may be prevented.

Rationale for the Budget Request

The 1987 budget request for this activity is $24,280,000, a decrease of $557,000 from the 1986 revised estimate. The decrease is related to program adjustments and indirect cost rate savings detailed in the General Statement. The requested level will fund 151 continuing and competing research project grants, 12 research careers, and 1 other research grant.

Research progress in this area is continuing to be made. Extensive studies have confirmed that synthetic pyrethroids (natural insecticides) are the most potent and safest insecticides for protecting crops from pest damage without risk to man or animals.

A prospective study on lead and children has shown that mental development at six months of age is negatively correlated with the degree of intrauterine lead exposure as reflected in the lead content of the mother's blood.

A study has demonstrated that singlet oxygen can react with polycyclic aromatic hydrocarbons to produce mutagenic products. A method for measuring singlet oxygen has been discovered which will allow for new investigations of the molecular events associated with environmental agents.

Respiratory distress syndrome in newborn infants during the neonatal period is under investigation. There may be many causes of this syndrome, but research to date suggests that some of the children may already have lung disease before they are born.

The mechanism of ozone damage to lung tissue is being explored. Animals exposed to ozone show effects that suggest that oxidant exposure may induce a sustained alteration in peripheral airway smooth muscle receptor mechanisms.

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987
Res. proj. grants				
Number	159	159	159	151
Amount	$ 25,132,000	$24,102,000	$24,102,000	$23,640,000
Other res. grants				
Number	15	15	15	13
Amount	799,000	735,000	735,000	640,000
TOTAL	25,931,000	24,837,000	24,837,000	24,280,000

National Institute of Environmental Health Sciences

Applied Toxicological Research & Testing

1987 Authorization: Indefinite

Budget Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$56,889,000	$54,361,000	$54,361,000	$54,492,000	$+131,000

Purpose and Method of Operation

This activity funds studies which characterize chemical toxicity and improve current test methods through research grants and research and development contracts.

The Toxicology Research and Testing Program (TRTP) is the National Institutes of Health's contribution to the National Toxicology Program (NTP). Primarily through contracts, this activity strives to develop and evaluate scientific information about potentially toxic and hazardous chemicals. This information is then used for protecting the health of the American people and for the primary prevention of chemically induced disease.

Rationale for the Budget Request

The 1987 budget request of $54,492,000 for this activity represents an increase of $131,000 over the 1986 revised estimate. The requested level will fund 24 continuing and competing research project grants, 5 research career awards, 1 other research grant, and 164 research and development contracts.

Progress in this area of research is continuing to be made. Studies on the interaction of lead and the red cell membrane have resulted in development of a more useful method for assessing low blood lead levels and provide insight into the biologic effects of lead exposure of the general population, lead workers and young children.

The importance of including immune function testing in the battery of tests for assessing toxicity of environmental agents has been emphasized with ongoing studies related to benzene toxicity. Mice exposed to low levels of benzene have exhibited changes in their immune function.

Two common urban pollutants, ozone and nitrogen dioxide, are increasing in concentration in some urban atmospheres. Ongoing studies have shown alterations in the lung mucocilliary clearance ability following exposure to these pollutants.

Immunological methods for the detection of alterations in DNA are being employed to quantitate the damage induced by exposure of DNA to ultraviolet light and a known carcinogen, ethylnitrosourea.

Projects were initiated in FY 1985 to compare tissue and species differences in the effects of chemical carcinogens on in vitro maintained human cells. These studies should provide a basis for determining the relationship between effects of chemicals on rodent cells and their implications for human cells.

In FY 1987, NIEHS plans to start approximately 10 to 15 comprehensive two-year toxicology and carcinogenesis studies and comprehensive prechronic (14 and 90 day) studies on selected chemicals and will continue test development and validation efforts. Efforts will focus on toxicological characterization of test chemicals.

There has been a world-wide effort over the past decade to develop short-term tests to supplement and perhaps eventually supplant whole animal tests to identify potential carcinogens. Such assay systems are reproducible, relatively inexpensive, quick, and provide valuable information on many biological properties of chemicals. NIEHS has taken the lead in formulating a highly objective approach to the difficult tasks of determining which assay systems, or combination of assays, are most effective in identifying potential carcinogens. Just as important, test systems (short-term as well as whole animal) should be able to identify and predict chemicals that do not cause cancer (noncarcinogens). The latter has been a major deficiency in other attempts to evaluate short-term test systems. It is only through an approach using both carcinogens and noncarcinogens and in which investigator bias is removed by testing and evaluating coded chemicals that science can make objective evaluations of assays or assay combinations. One other important aspect of this work is to understand the mode of action of carcinogenic chemicals that act through nongenetic mechanisms and to attempt to find ways to identify these using short-term tests.

The National Academy of Sciences recently identified reproduction and development as one of six areas where more research is critically needed. One of the largest voids in this area is knowledge of the effect of chemicals on male reproduction. To address this need, NIEHS has implemented the following approach for these studies: (1) the function of the reproductive system as a whole is being evaluated after exposure to a given chemical in mating studies using rodents; (2) if an effect is seen in these mating studies, an effort is made to determine what part of the male reproductive system is affected and in particular how testicular lesions develop, which cell in the testis is affected, and if hormonal systems are involved; and 3) focus on specific cell types, subcellular functions and mechanisms of actions.

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The NIEHS continues to assess the potential and extent of various environmental pollutants that cause secondary immunodeficiency disease and allergic hypersensitivity. Efforts are underway to assess the presence and extent of immunotoxicity resulting from exposure to selected chemicals. The potential of these chemicals to influence immune function (host defense) as well as to act as allergens (hypersensitivity) is being investigated. The ultimate goal of these studies is to determine whether such exposure to various chemicals represents a potential human health hazard.

The semiconductor microelectronics industry is of increasing public health interest because of its continuing rapid expansion, exposure of workers to low level mixtures of some unusual but extremely toxic inorganic chemicals, and a high percentage of women in the workforce. Primary concern is currently focused on assessing potential risk of systemic toxicity produced by interactive effects between these chemicals in a highly sensitive subpopulation. Special emphasis is being placed on continuing development of non-invasive early biological indicators of cell injury to detect chronic low-level toxicity from these agents in target organ systems under multi-element exposure conditions.

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987
Res. proj. grants				
Number	24	24	24	24
Amount	$ 3,868,000	$ 3,651,000	$ 3,651,000	$ 3,539,000
Other res. grants				
Number	6	6	6	6
Amount	498,000	528,000	528,000	528,000
R&D contracts				
Number	172	162	162	164
Amount	52,523,000	50,182,000	50,182,000	50,425,000
TOTAL	56,889,000	54,361,000	54,361,000	54,492,000

National Institute of Environmental Health Sciences

Biometry and Risk Estimation

1987 Authorization: Indefinite

Budget Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$5,943,000	$5,698,000	$5,698,000	$5,307,000	$-391,000

Purpose and Method of Operation

This program supports research grants and contracts that typically involve laboratory-based, statistical or epidemiological studies of environmentally-related diseases. Areas of emphasis include the development of both data resources and statistical and epidemiological methodology useful in the evaluation of potential human health risks.

Grant related research focuses on investigator initiated activities such as the development of statistical procedures applicable to design analysis and interpretation of laboratory carcinogenicity studies; development of a method of estimating the degree of human exposure to organic chemical contaminants for use in epidemiological studies; and epidemiologic studies on the effects of exposure to air pollutants. Contract research focuses on directed activities such as the development of a computerized carcinogenesis database used, for example, to investigate various issues bearing on species extrapolation.

Rationale for the Budget Request

The 1987 budget request of $5,307,000 for this activity represents a decrease of $391,000 from the 1986 revised estimate. The decrease is related to program adjustments and indirect cost rate savings detailed in the General Statement. The requested level will fund 11 continuing and competing research project grants, 1 other research grant, and 4 research and development contracts.

During the past fiscal year the carcinogenic potency database developed under the Interagency Agreement with the Department of Energy was updated to incorporate all published studies through 1983 that satisfied the study inclusion criteria. In addition, a number of research projects utilizing the database were initiated, continued, or completed. For example, a study of the potential association between carcinogenic potency and various parameters of rodent tumor pathology (such as tumor site, whether or not tumors metastasized, etc.) was completed. Current efforts include an additional updating of the database, further exploration of the relationship between toxicity and carcinogenic potency, and the evaluation of the rodent TD_{50} (potency) index in terms of human exposure levels.

A study of female hormones produced during the menstrual cycle may provide insight into the mechanisms by which environmental toxins interfere with fertility. This study uses urine collected daily from 230 women who are trying to become pregnant. Urinary excretion of estrogen and progesterone products will be compared for cycles in which women do not conceive and cycles in which pregnancy occurs. Special attention will be given to the disruption of these cyclic hormones by substances that might impair fertility.

Studies on the effects of indoor and outdoor air pollution on pulmonary function of adults and children in six cities is continuing. Recent analysis of data suggests that exposure to a moderately elevated concentration of air pollutants, namely sulfur dioxide, suspended sulfates, and total suspended particulates, may increase risk for bronchitis and other respiratory disorders for pre-adolescent children.

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987
Res. proj. grants				
Number	11	11	11	11
Amount	$ 3,973,000	$ 3,758,000	$ 3,758,000	$ 3,667,000
Other res. grants				
Number	2	1	1	1
Amount	50,000	20,000	20,000	20,000
R&D contracts				
Number	6	6	6	4
Amount	1,920,000	1,920,000	1,920,000	1,620,000
TOTAL	5,443,000	5,698,000	5,698,000	5,307,000

National Institute of Environmental Health Sciences

Resource and Manpower Development

1987 Authorization: Indefinite 1/

Budget Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$23,893,000	$22,865,000	$22,865,000	$22,488,000	$-377,000

1/ Authorization for research training totals $260,000,000 in 1986 for NIH ADAMHA, and HRSA.

Purpose and Method f Operation

NIEHS currently supports Resource and Manpower Development through three major grant programs: Environmental Health Sciences (EHS) Core Centers; Marine and Freshwater Biomedical Sciences Specialized Centers of Research (MFBS SCORs); and research manpower development programs.

Through the support of centers, it is possible to assemble a critical mass of scientific talent and apply it to the complex scientific questions which typify all environmental health problems. Because of the inherent flexibility of the grants, the centers can respond to emerging environmental health research needs.

The EHS centers, which provide long-term support for multidisciplinary environmental health research, have helped clarify the scope of many environmental health problems and outlined future research and manpower needs. The focus of each of the centers is unique and together they represent a vital national resource for research and manpower development in the environmental health sciences. The individual centers deal with one or more broad scientific areas such as occupational and industrial health, heavy metal toxicity, agricultural chemical hazards, and air, water and food pollution. They also deal with specific scientific problems such as how environmental factors cause cancer and birth defects, basic toxicity mechanisms, behavioral anomalies, respiratory and cardiovascular diseases, specific organ toxicology, body defense mechanisms, and injury modulation factors such as age, nutrition, and genetic makeup.

The goal of the MFBS centers is to use aquatic systems as models of human systems to determine mechanisms of chemically-induced diseases. These systems are often easier to study than mammalian (rat, mouse or primate) models and results are as useful.

NIEHS is the only Federal agency with a major program which supports training scientists for careers in basic and applied research needed to determine the risks associated with exposure to chemicals. NIEHS supports training in toxicology, pathology, mutagenesis, epidemiology, and biostatistics. Programs are offered to support veterinary pathologists and to train clinicians as environmental epidemiologists.

Rationale for the Budget Request

The 1987 budget estimate for this activity is $22,488,000, a decrease of $377,000 from the 1986 revised estimate. The Institute will support 10 EHS centers, 5 MFBS centers, and 442 research trainees in 1987.

Scientists studying the health effects of fossil fuels utilization are developing analytical methodology to determine which environmental chemicals actually enter the body and cause changes in the cell's genetic structure. Human blood samples are used to determine exposures to chemical hazards, and urine samples are analyzed for degradation products of DNA, indicating that damage has occurred. These advances in analytical biochemistry and analytical kinetics are first steps toward direct studies of the effects of environmental chemicals on humans, as they avoid the uncertainties of extrapolation from experimental animals to man.

Scientists are developing tests for evaluating the effects of air pollutants on the human lung. An aerosol dispersion test was found to be more sensitive than standard respiratory function tests as a means of distinguishing affects of exposures to air pollutants as demonstrated by differences found between young adult smokers and non-smokers. The utilization of the test for evaluating the effects of passive smoking, for analyzing the impact of air pollutants other than cigarette smoke, and for detecting respiratory diseases of different types at pre-clinical stages in their development is being explored.

The mechanisms by which chemicals produce acute toxic effects in biological systems are not well understood. With a focus on liver cells, defense mechanisms against chemically induced acute toxicity are under investigation. The role of antioxidants, glutathione, and vitamin E are being studied as it has been found that vitamin E in the cell has a protective effect even when the cells natural glutathione is diminished or exhausted. Other studies are focusing on toxic effects on the cell membrane which may be targets for many environmental toxicants or their metabolites.

Scientists have discovered a new disease in persons exposed to toxic pollutants in the atmosphere. This is called reactive airway dysfunction syndrome and results from a nonspecific sensitization of the muscles of the air passages to irritants. This sensitization results in a chronic disease involving restricted breathing which in its more pronounced form is expressed as severe asthma. Ongoing studies are pointing to ways of identifying the disease in its earliest forms and preventing its progress.

Another study is investigating dietary constituents which may modify the actions of carcinogens. Researchers found that a new antioxidant, indol-3-carbinol, a natural dietary constituent, suppresses the metabolism of carcinogenic chemicals and inactivates the dangerous chemicals produced by such metabolism. Similarly, researchers have isolated a compound from soybeans which has the ability to completely inhibit transformation of normal cells to cancer cells in culture at very low, non-toxic concentrations. This effect has also been observed in experimental animals where the appearance of intestinal cancer, brought on by a known chemical carcinogen, was completely inhibited by the addition of this extract of soybeans to the diet.

Researchers have developed a method for measuring by-products of DNA damage in urine of experimental animals and in man. This method may be useful in determining both background and environmental exposures to carcinogenic chemicals.

A modest beginning has been made in the new training programs, clinical investigator awards (CIA) and physician scientist awards (PSA), mentioned at last year's hearings. To date, three individual PSAs have been made to allow the training of M.D.s in basic research methodologies. One institutional award was also made. Four individual CIAs to support physicians for further training in clinical environmental health sciences have also been awarded.

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987
Res. Centers				
Number	15	15	15	15
Amount	15,391,000	14,729,000	14,729,000	14,482,000
Res. Training				
Individual				
Number	38	36	36	33
Amount	710,000	679,000	479,000	670,000
Institutional				
Number	439	439	439	409
Amount	7,792,000	7,457,000	7,457,000	7,336,000
Subtotal trng.				
Number	477	475	475	442
Amount	8,502,000	8,136,000	8,136,000	8,006,000
TOTAL	23,893,000	22,865,000	22,865,000	22,488,000

National Institute of Environmental Health Sciences

Intramural Research

1987 Authorization: Indefinite

Budget Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$54,169,000	$51,801,000	$51,801,000 (FTEs: 579)	$52,647.000 (579)	$+846,000 (--)

Purpose and Method of Operation

Research in this budget activity includes: (1) the biological basis of toxicology studied through the disciplines of biochemistry, pharmacology, molecular biology, genetics, and cell biology focusing on problems in reproductive biology, neurobehavioral systems, and on pulmonary cellular pathology, (2) the application of biological tests for toxicity and the development of new methodology that exploits advances in technology and knowledge including research on the detection of chemical carcinogens, mutagens, and evidence of organ system damage; and (3) biostatistical, biochemical and epidemiological studies that generate information and methodology applicable to the evaluation of health risks posed by exposure to chemical hazards.

Basic and applied research is conducted by NIEHS scientists in three interrelated program areas. Scientists in the Intramural Research Program (IRP) concentrate their efforts on understanding the mechanisms by which the environment alters the body's normal functions. The theme underlying their research efforts is based on the fact that the body's functions are fundamentally controlled by complex interactions among four basic communication networks: the brain or neuroendocrine system; the immune system; the reproductive system; and the hormone or endocrine system that governs the structure and function of all other tissues in the body. Each of these systems communicates with the other in a moment to moment, reversible (dynamic) fashion in response to the ever-changing set of environmental signals (light, sound, touch, chemicals) that act upon various parts of the body. When all is working properly, the communicating systems respond in an integrated fashion inducing adjustments in literally every part of the body down to the minutest component of each cell. Often, however, continual challenges from environmental insult cause corrective responses within the body to become difficult or even impossible, often leading to a debilitating disease or, if the change is irreversible, death.

To illustrate the complexity of the problems encountered using simple cellular systems and the recent discoveries that may lead to solutions, it has been found that man-made toxic agents such as phorbol esters and diethylstilbestrol (DES) mimic the actions of many growth-promoting hormones but in ways that lead to abnormal growth of the cultured cells. Phorbol esters, tumor promoters, are structural counterparts to fatty substances that normally serve as mediators of growth-promoting hormones. However, unlike the normal counterparts, the phorbol esters are not metabolized by the host cell. From such findings it is apparent that the dynamics of hormone action must be an important determinant in whether the products of their actions can lead to normal or abnormal actions. DES is metabolizable by cells. However, depending on the type of cell and other factors, its metabolism can lead to the production of powerful chemical-modifying agents, called free radicals, that can alter the structure and function of many cellular constituents, including the DNA that makes up the genetic apparatus of cells. In fact, at higher amounts, sex steroids can give rise to the same products with similar consequences. Such findings suggest that alterations of the levels of free radicals in cells may be of potential usefulness for preventing the actions of both man-made toxic agents as well as the normal constitutive hormonal agents produced by one or more of the communicating systems involved in the integration of bodily functions.

The Toxicology Research and Testing Program (TRTP) studies chemicals of potential hazard to humans and develops relevant methodology to establish earlier, less costly ways to determine toxicity of various types. Most current methods are expensive and time-consuming. The large number of new chemicals entering the market place each year makes it imperative that more efficient means of determining safety be developed. The TRTP uses a comprehensive approach to studying chemicals in which numerous end points are examined rather than merely observing a single result such as carcinogenicity. There is increasing interest in the ability of environmental agents to affect genetic material, the reproductive process and other major organ systems. Some chemicals may also have unfavorable effects on the immune system, making humans more susceptible to infectious disease. TRTP scientists are devising more sensitive testing methods and are attempting to gain a greater understanding of apparent differences in the response to chemicals by different species and sexes.

The Biometry and Risk Assessment Program (BRAP) plans and conducts research in the areas of quantitative and biochemical risk assessment, statistics, biomathematics, and epidemiology. Program staff members also collaborate with scientists in other Institute programs and provide a central resource for automated data processing capability. Within the BRAP, the Statistics and Biomathematics Branch pursues a broad research effort in a variety of areas including the design and analysis of carcinogenicity experiments, statistical studies in genetic toxicology, mathematical modeling of biological processes, and risk assessment methodology development. The Laboratory of Biochemical Risk Analysis is primarily concerned with the development of laboratory procedures for quantifying exposures in terms of the biologically effective dose, and with the application of these procedures to human population monitoring and extrapolation of toxicologic outcomes across species. The Epidemiology Branch investigates a spectrum of adverse health effects that may be induced by exposure to various environmental agents. Such health effects include impairment of reproduction and development as well as the onset of specific chronic diseases.

Rationale for the Budget Request

The budget request for Intramural Research is $52,647,000, an increase of $846,000 over FY 1986. Mandatory increases of $1,655,000 will necessitate program adjustments, but efforts will be made to protect direct laboratory research. Among the more promising projects to be pursued in FY 1987 are:

- Asbestos and certain glass fibers, when inhaled in lungs, can induce both scarring of lung tissue and tumors. Brief exposure of lungs to these substances has been shown to induce scavenger cells (macrophages) to congregate at the sites of deposition of the particles. The macrophages produce, as a result, sufficiently large quantities of growth-promoting factors that induce enhanced growth of connective tissue-producing cells. This may be the mechanism involved in lung scarring. Tumor production seems to be the result of uptake of the fibers within pulmonary cells followed by damage of the nuclear chromosomes and of the normal processes of mitosis. Interestingly, DES uptake by cells can lead to the same type of disruption of chromosomes seen with asbestos, glass fibers, and by silica. Thus, free radical production from DES metabolism seems to lead to the same tumor-promoting effects as the cellular ingestion of particles. These findings indicate that both chemical and physical (particle intake) environmental factors can induce common harmful effects, possibly through similar pathways, on the living process. These studies will continue.

- Luteinizing hormone (LH), an essential hormone released by the pituitary gland, is responsible for regulating the development, growth, and functions of the reproductive system. Its release from the pituitary gland is governed by a number of stimuli produced in the brain and involves the amount of free calcium in the cells responsible for synthesis and secretion of the hormone. Of major importance to the functions of LH is the pulsatile or oscillating pattern of release of LH from the pituitary rather than simply the amount released, as older concepts suggested. Understanding the mechanism of pulsatile release mechanisms and why such mechanisms are essential for the normal actions of LH in man are important new research areas.

- Syrian hamster embryonic cells have proven to be an excellent model for investigating the various factors that lead to uncontrolled cellular growth and tumors. A crucial factor hitherto not considered in the multiple factors required for tumor development are recently discovered suppressor genes that, in normal cells, prevent or inhibit the ability of carcinogens and various oncogenes to express their growth-promoting activities. Detection and isolation of suppressor genes is a major new research undertaking which will lead to both a better understanding of the factors that influence uncontrolled cellular growth and may lead to methods for reversing such growth and thus tumor formation.

- Following the accidental release of methyl isocyanate from a pesticide plant in India, and the subsequent deaths and injuries of thousands of people, the NIEHS developed and implemented a series of studies designed to examine the long-term health effects of acute short-term exposure to the chemical. Using rats and mice, studies were performed to examine respiratory and systemic toxicity following 2-hour inhalation of lethal and sublethal concentrations, and to examine specific effects of immune, reproductive and genetic function following 4-day exposure to lower concentrations. The results of these studies will be issued in March 1986. In addition, the carcinogenic potential is being assessed in studies of both conventional and unconventional design; for example, 2-year repeated dose studies, and 2-year studies following a single exposure to near lethal concentrations.

- A Quality Assurance unit has been established at NIEHS to provide a program for tracking, inspecting and auditing of all studies conducted by the TRTP. This unit is critical to assuring the accuracy and validity of studies and to manage and oversee auditing of studies conducted by contractors.

- The bias and estimated variance of an index of carcinogenic potency, the TD_{50}, is being evaluated for a variety of dose-response patterns commonly encountered in carcinogenesis screening studies in order to assess its potential usefulness. Furthermore, since the most appropriate determination of relative carcinogenic potency should depend on the shapes of the dose-response curves for the chemicals or species being compared as well as on their estimated TD_{50} values, a recently developed procedure for differentiating between linear and non-linear curvature is also being assessed.

- Serial blood samples are being collected from women before, during and after chemotherapy for breast cancer. These samples offer an opportunity to observe the kinetics of genetic damage in humans following precisely characterized exposures. Genetic damage will be monitored by the incidence of chromosomal aberrations and sister chromatid exchanges (SCEs). The use of more experimental assays of gene toxicity such as glycophorin mutation are also being considered.

- There is considerable controversy regarding the influence of route of exposure of benzene on the toxicity of this compound, particularly its carcinogenic effects. Laboratory scientists are addressing this question by performing pharmacokinetic studies in animals exposed to benzene either by the oral or inhalation route. These investigations use a wide dose-response range including exposures as low as those encountered in the workplace. Key metabolites are quantified in target tissues and blood and cytogenetic effects are evaluated in relation to the pharmacokinetic and metabolism data. Follow-up studies will determine if DNA adduct concentrations are dose dependent. These studies should enhance the ability to predict more accurately the risk of benzene toxicity in occupationally-exposed individuals.

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National Institute of Environmental Health Sciences

Research Management and Support

1987 Authorization: Indefinite

Budget Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987	Increase or Decrease
$ 6,043,000	$ 5,743,000	$ 5,743,000	$ 5,805,000	+$ 62,000
		(FTEs: 81)	(81)	(--)

Purpose & Method of Operation

Research Management and Support is the budget activity that provides salary and other expenses for those employees charged with the overall direction of the Institute and with the scientific review and management of the grant and contract programs. Included in this activity are components of the Office of the Director and of the Office of Administrative Management, and all of the Extramural Program. In addition to providing assistance and advice to the Director in managing the Institute and its resources, staff funded by this activity perform various functions such as financial and personnel management, planning and evaluation, and the management of the peer review process and coordination of international activities. Also included are the central staff required to coordinate and manage the National Toxicology Program (NTP). The NTP is composed of elements of the Centers for Disease Control, the National Center for Toxicological Research, the National Institute of Occupational Safety and Health, and the National Institute of Environmental Health Sciences.

Rationale for the Budget Request

The 1987 request of $5,805,000 represents an increase of $62,000 over the 1986 revised estimate. Program adjustments will be made in such areas as travel, printing and reproduction, supplies and materials, and general-use equipment in order to affect mandatory increases of $109,000.

One of the primary goals of the Office of the Director during this year will be to analyze the various Institute programs and supporting services to increase productivity and efficiency and avoid waste and unnecessary duplication. Through the use of automation and with increased training and emphasis at all levels of management, the Institute expects to realize savings in both personnel and dollars. A newly formed Productivity Committee, comprised of staff from all levels and programs, has begun to review each of eight major administrative areas, such as procurement, personnel, facilities maintenance, etc.

The Institute plans to make increased use of the Program Announcement and Request for Applications mechanisms during FY 1987. By more use of these notices, extramural investigators can be encouraged to pursue projects in areas identified by advisory groups and staff as understudied or having high promise. At the same time, unsolicited grant applications will continue to be awarded after peer review by outside scientific review bodies.

The Institute initiated one new Environmental Health Sciences center and two new Marine and Freshwater Biomedical Sciences centers in FY 1985. These new centers will be closely watched during their early years to ensure that they continue the same standard of excellent research characterized by the existing centers. The centers have proven to be an invaluable resource not only for the science they do, but also for the many young scientists they train.

The role of the Institute in working with other countries concerned about the environment has been expanding. Scientists from the Institute and grantees supported by NIEHS are participants at international meetings where problems of mutual interest are discussed and studied. Through the United States-Japan Cooperative Science Agreement and other international cooperative projects, scientists from around the world work together to try to understand how various environmental factors affect us all. There is a growing realization that environmental concerns are not bound by national borders. Working with the World Health Organization and others, Institute scientists are dealing with problems arising from the increased use of pesticides and other chemicals in developing countries.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of Environmental Health Sciences

DETAIL OF PERMANENT POSITIONS

	1985 Actual	1986 Estimated	1987 Estimated
ES-4	10	10	10
ES-3	1	1	1
Subtotal	11	11	11
GS/GM-15	19	19	19
GS/GM-14	50	50	50
GS/GM-13	61	61	61
GS-12	46	46	46
GS-11	28	28	28
GS-10	1	1	1
GS-9	80	80	80
GS-8	4	4	4
GS-7	60	60	60
GS-6	55	55	55
GS-5	61	61	61
GS-4	42	42	42
GS-3	11	11	11
GS-2	1	1	1
Subtotal	519	519	519
Grades established by Act of July 1, 1944 (42 U.S.C.207):			
Assistant Surgeon General	1	1	1
Director Grade	6	6	6
Senior Grade	6	6	6
Full Grade	4	4	4
Subtotal	17	17	17
Grades established under sec.208(g) of the Public Health Service Ace (42 U.S.C.210(g)	1	1	1
Ungraded	72	72	72
Total permanent positions	620	620	620

WEDNESDAY, MARCH 12, 1986.

NATIONAL INSTITUTE OF DENTAL RESEARCH

WITNESSES

DR. HARALD LÖE, DIRECTOR

DR. THOMAS MALONE, DEPUTY DIRECTOR, NIH

DR. MARIE U. NYLEN, ASSOCIATE DIRECTOR, EXTRAMURAL PROGRAM, NIDR

DR. DUSHANKA V. KLEINMAN, SPECIAL ASSISTANT TO THE ASSOCIATE DIRECTOR FOR PROGRAM COORDINATION, EPIDEMIOLOGY AND ORAL DISEASE PREVENTION PROGRAM, NIDR

DR. LOIS A. SALZMAN, SPECIAL ASSISTANT TO THE DIRECTOR, INTRAMURAL RESEARCH PROGRAM, NIDR

GILBERT D. PRESS, BUDGET OFFICER, OFFICE OF THE DIRECTOR, NIDR

DENNIS P. WILLIAMS, ACTING DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. NATCHER. We take up next the National Institute of Dental Research.

We have before the Committee Dr. Harald Löe, the Director. Dr. Löe, it is a pleasure to have you back before the Committee again.

Before you proceed with your statement, if you will, please, tell us who you have there at the table with you.

Dr. LÖE. Thank you very much, Mr. Chairman. It is always a pleasure to come back to this Committee. With me today to my far left is Dr. Lois Salzman, who is the Assistant to the Director for the Intramural Research Program. Next is Dr. Dushanka Kleinman, who is the coordinator of the Epidemiology and Oral Disease Prevention Program.

Next is Dr. Marie Nylen, who is the Associate Director for the Extramural Program. Then next to me here is Mr. Gilbert Press, who is the Budget Officer of the Institute.

Mr. NATCHER. Thank you very much. We are delighted to have all of you before the Committee. Dr. Löe, we will be pleased to hear from you at this time.

Dr. LÖE. Mr. Chairman, in addition to my written statement, I would like to make four major points about NIDR activities this year. They concern the Institute's use of large grants and center mechanisms, specific advances coming from cellular and molecular biology, and new initiatives in AIDS and in aging research.

In considering our Fiscal Year 1985 budget, this Committee asked the NIDR to elicit the broad consultation of the dental research community in developing plans for the use of centers and other large grant support mechanisms, and so we did. We convened a 20-member panel representing our advisory bodies, grantees, center directors and representatives of professional groups, and the panel sought the advice and opinions of other governmental agencies and professional organizations and the dental community at large.

Subsequently, in October 1985, the NIDR prepared a report to this Committee in which we indicated our plans for the use of centers and other large grants. We essentially followed the panel's advice in preparing this report and concurred in almost all of their recommendations.

Mr. Chairman, this exercise proved to be an extremely valuable one in forging closer ties between the Institute and its constituencies. I would like to take this opportunity to commend this Committee for its wisdom and for its advice and guidance in urging this approach.

I am pleased to announce that the NIDR has issued a request for applications for new Research Centers in Oral Biology. There is open competition for these centers, and applications will be subject to rigorous peer review.

The Program Announcement has been met with great enthusiasm by the research community, and we expect keen competition among a large number of applicants.

Now, my second highlight concerns the pace and the progress that we are seeing in dental research as a result of using cell and molecular techniques. These new methods are significantly accelerating the movement from basic knowledge to clinical application.

You may remember that genetic engineering techniques were applied in the development of an experimental oral herpes vaccine that I reported on last year. Further work on the vaccine has established that mice vaccinated last year are still protected. This is the first demonstration of the duration of effectiveness of a recombinant vaccine.

The investigator who played a leading role in the development of the herpes vaccine, Dr. Abner Louis Notkins, is the Director of our Intramural Research Program. He is not able to be with us today. He is in the Federal Republic of Germany to receive the prestigious Paul Ehrlich Award for 1986, an award amounting to $40,000 and a gold medal which will be given to him by the President of West Germany for his outstanding work in the fields of immunology, microbiology and chemotherapy.

I have provided Mr. Neil with copies of the announcement of this award, and with your permission, sir, I would like the announcement incorporated into the record.

Mr. NATCHER. Without objection, it is so ordered.

[Information follows:]

NIDR
Research
News

NATIONAL INSTITUTE OF DENTAL RESEARCH

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health
Bethesda MD 20205

March 3, 1986 Jody Dove - 301-496-4261

DR. ABNER LOUIS NOTKINS TO RECEIVE 1986 PAUL EHRLICH PRIZE

Dr. Abner Louis Notkins, director of intramural research for the National Institute of Dental Research (NIDR), one of the National Institutes of Health, has been selected to receive the prestigious 1986 Paul Ehrlich and Ludwig Darmstaedter Prize. This prize is awarded annually by the Paul Ehrlich Foundation in the Federal Republic of Germany for outstanding work in the fields of immunology, microbiology, or chemotherapy.

The Foundation selected Dr. Notkins as this year's recipient in recognition of his pioneering work on viruses and autoimmunity while at NIDR. The award, of approximately $40,000 and a medal, will be presented in Frankfurt on March 14, the birthday of Paul Ehrlich. Considered one of the founding fathers of modern immunology, Dr. Ehrlich received the Nobel Prize in 1908 for his work on diphtheria toxin. A year later, he developed Salvarsan, the first drug treatment for syphilis. The two-day Ehrlich award ceremony, which is attended by the President of Germany, will include a dinner hosted by the Prime Minister of Hessen in honor of Dr. Notkins. Dr. Notkins is only the second person in the last 20 years to be the sole recipient of the award.

The Paul Ehrlich Foundation was established in 1929, and the award has been given annually since 1952. Recipients of the award are selected by a 15-member international committee. Past winners include a number of Nobel Laureates.

Among his many achievements, Dr. Notkins has elucidated mechanisms involved in the pathogenesis of viral and endocrine diseases. In his early work, he concentrated on persistent infections and showed how the immune response to viruses caused tissue injury. Over the past decade, he has focused on the role of viruses and autoimmunity in endocrine diseases, especially insulin-dependent diabetes mellitus.

Dr. Notkins is internationally recognized for his contributions to diabetes research. In experimental animals, he showed that viruses could produce diabetes by destroying insulin-producing beta cells, that susceptibility was genetically controlled, and the disease could be prevented by a vaccine. He then extended his work to humans, showing that occasional cases of insulin-dependent diabetes could be triggered by viruses. Recently, he has been tracking factors such as autoantibodies that might be involved in endocrine diseases and has developed methods for making and studying human monoclonal autoantibodies.

Last year, Dr. Notkins led a team of researchers from NIDR and the National Institute of Allergy and Infectious Diseases in developing an experimental herpes vaccine that prevents the virus from establishing a latent infection. The genetically engineered vaccine, which was tested successfully in laboratory mice, is targeted against herpes simplex virus (HSV) type 1, the virus responsible for cold sores. There is evidence the vaccine also may be effective against HSV type 2, or genital herpes. Further animal studies are underway, in preparation for human testing of the vaccine.

After receiving his B.A. from Yale and an M.D. from New York University, Dr. Notkins served an internship and residency in internal medicine at The Johns Hopkins Hospital. In 1960 he joined the National Institutes of Health as a research associate at the National Cancer Institute. The following year he moved to the NIDR, where he later became chief of the Laboratory of Oral Medicine in 1973. In 1985 he was appointed Director of the NIDR Intramural Research Program, while also retaining his role as lab chief.

Dr. Notkins has published and lectured extensively throughout the world in the fields of viral immunology and immunopathology, as well as on the role of autoimmunity in diabetes mellitus and related disorders. He has received numerous commendations throughout the course of his research career, including the 1980 David Rumbough Scientific Award of the Juvenile Diabetes Foundation for investigative excellence in diabetes, a Department of Health and Human Services Meritorious Service Medal in 1973, and a Distinguished Service Medal in 1981. Dr. Notkins was also the first recipient of the Paul E. Lacy Research Award presented by the National Diabetes Research Interchange. In 1982 he was elected to the prestigious Association of American Physicians.

Mr. CONTE. Is that $40,000 before Gramm-Rudman or after Gramm-Rudman? [Laughter.]

Dr. LÖE. That is excluding any interference by Gramm-Rudman.

Now, cell and molecular biology methods applied in bone research are allowing us to sample bone-forming cells from healthy people and from patients with osteoporosis, osteoarthritis and any other bone disease. We can culture these cells in a laboratory dish and watch their behavior over periods of weeks or months as a clue to pathology. We have also isolated and purified a small protein we call osteogenin, believed to be an active factor in the formation of new bone following bone fracture or bone loss.

Another example of progress at the molecular level is thoroughly novel. It concerns the discovery of the active ingredient of a glue that the marine animal, the common mussel, uses to stick to rocks and to the keels of ships. The significance of this glue is that it works in water and in body fluids like blood and saliva, where no manmade adhesive has yet to work. One of our grantees has been able to single out the key protein in this substance. Now there are plans to manufacture the glue using genetic engineering methods for widespread applications—as a sealant and filling material in dentistry, as an aid in muscle, tendon and bone attachment in orthopedic surgery, and, with slight change in the formula, as a possible coating for ship bottoms to prevent attachment by marine animals.

This year the NIDR is expanding its research on AIDS as more and more information is accumulating on the role that oral opportunistic infections play in the natural history of this disease. We have made important immunological findings and are moving on to analyses of changes in oral tissues and in oral fluids.

The major steps in the NIDR initiative to improve oral health in the aging population have begun. Later this year we will announce preliminary results of the most comprehensive oral health survey conducted in America. The data will provide up-to-date documentation on the extent of the various types of tooth decay, periodontal diseases and other oral conditions in adults, based on examination of 20,000 Americans seen in the workplaces and in the centers for the elderly around the country.

We are encouraging the profession and the research community to address the needs of older Americans, and we will be releasing on Friday, March 14, at the annual meeting of the American Association for Dental Research here in Washington, a new Research Agenda on Oral Health in the Elderly, developed jointly by the NIDR, the National Institute on Aging, and the Veterans Administration. Again, I have provided copies of this Agenda to Mr. Neil.

More and more we are emphasizing the importance of science information and technology transfer to promote the adoption of new preventive and treatment regimens by the public and by the profession. We began to get that message across with the early work on fluorides. The process has continued with the demonstration of the effectiveness of dental sealants to protect children's teeth from decay.

Now we are saying that prevention is not just for children any more. We are reaching out to all adults with a message that research has shown that teeth can be maintained for a lifetime—provided that they are cared for.

Mr. Chairman, the Fiscal Year 1987 budget for the NIDR is $96,482,000. I will be pleased to answer any questions.

Mr. NATCHER. Thank you very much, Dr. Löe.

[Statement follows:]

Statement of Dr. Harald Löe

Each year it has been my pleasure to describe current Institute accomplishments and initiatives and put them into the perspective of our Long-Range Research Plan FY 1985-1989, Challenges for the Eighties, published in 1983. In the Plan we affirmed the continued need to emphasize basic research as a key to understanding the oral tissues and their problems. To underscore that commitment we observed that dental investigators were quick to adopt the new techniques of cell and molecular biology, in particular, recombinant DNA and monoclonal antibody methods, to attack long-standing problems.

It is gratifying to report now how rapidly this "molecularization" of biology is transforming dental research. Moreover, the new technology is achieving another Institute goal stated in the Plan: accelerating the movement of laboratory findings to clinical applications.

This year we saw major gains in mineralized tissue research. Earlier studies of bones and teeth have paid off in important discoveries concerning collagen, tooth enamel, and the cells and extracellular factors that regulate the growth, maintenance and repair of mineralized tissues. Now, for the first time, NIDR scientists have perfected cell culture techniques that are permitting long-term studies of the behavior of normal and diseased bone cells in a laboratory dish. The scientists are studying cells from patients with all kinds of bone disease, from the hereditary "brittle bone" diseases like osteogenesis imperfecta, to the crippling diseases that affect so many older Americans--osteoarthritis and osteoporosis.

These same investigators have also cloned the genes that code for two important proteins involved in bone metabolism. Monoclonal antibodies have been raised to these proteins and the investigators are using the antibodies and other probes to compare osteoporotic bone tissue with normal tissue in search of clues to the pathologic process.

Another exciting development has been the isolation and purification of a small protein, called osteogenin, believed to be an active factor inducing new bone formation following bone fracture or loss. Plans now call for an NIDR-industry collaborative effort to characterize the protein fully, with the hope of using recombinant DNA methodology to produce osteogenin in quantity for use in reconstructive surgery.

Studies of saliva are another area where dental investigators have long had a claim to fame, demonstrating the many ways in which saliva works to preserve and protect the oral tissues. This year NIDR investigators solved the puzzle of how water and salt are taken up by salivary cells and how the fluid, along with other ingredients, is later secreted in the form of saliva. These discoveries have led to new classifications of patients who suffer the painful symptoms of dry mouth, a condition that predisposes to a variety of oral infections, including tooth decay and gum disease. These individuals represent a surprisingly large group that includes people with specific glandular and rheumatological disorders, patients who have undergone radiation and chemotherapy for cancer, and many adults who take daily medications with a side effect of oral dryness. Tests developed by the NIDR scientists now show that in some of these people the salivary cells are still able to take up salt and water but are blocked in secreting the end product, saliva. That observation has led to the experimental use of the drug pilocarpine which has proven to be a safe and effective means of unblocking the secretory channels and restoring the flow of saliva.

A third example of the molecular revolution in dental research concerns vaccine development. Last year we reported the success of a genetically engineered vaccine against herpes simplex virus type 1 (HSV 1), the cause of the oral lesions called cold sores. The vaccine, composed of the vaccinia virus and a gene coding for a surface antigen of the herpes virus, provided immunity to infection by HSV 1 in mice, as well as substantial protection against HSV 2, the cause of genital herpes. Further, the vaccine protected against latent infection in the majority of cases. Now, one year later, the scientists have shown that the vaccine continues to provide immunity in the animals. This is the first demonstration of the duration of effectiveness of a recombinant vaccine and gives further impetus to animal testing in anticipation of human trials.

The Institute also continues to support work on an anti-caries vaccine. The ability to use genetic engineering methods to isolate and purify potential immunizing molecules from Streptococcus mutans, the bacteria considered the principal cause of dental caries, has increased activity in this area. This research has also attracted nondental investigators to the study of dental caries as a model of an infectious disease that can shed light on little-understood aspects of host-pathogen interactions. One such aspect concerns "secretory" immunity, a host defense mechanism in which disease-fighting antibodies are incorporated into the saliva that is secreted in the oral cavity. Several researchers have also suggested a new biotechnology approach to caries prevention. They propose that monoclonal antibodies targeted to S. mutans antigens be produced and then applied locally in the mouth to provide passive immunity to dental caries.

Oral infections have taken on special significance in dental research with the advent of acquired immune deficiency syndrome (AIDS). NIDR grantees have found growing evidence that the oral cavity is a frequent site of the serious opportunistic infections and of the Kaposi´s sarcoma associated with AIDS. Moreover, the need to treat oral conditions in AIDS patients and to adopt measures to ensure that both dental personnel and the general public are protected against exposure to the AIDS virus has been imperative.

Several NIDR-supported investigators have now identified specific oral lesions that may precede the frank clinical picture of AIDS. Changes in salivary components may occur even earlier. For example, a family of proteins normally present in saliva is known to inhibit the growth of the fungus that causes candidiasis. Clinical experience with AIDS suggests that if candidiasis develops in individuals at risk for AIDS, it is highly likely that these individuals will go on to develop AIDS.

NIDR will expand research on AIDS, building on these observations. Researchers will document the sequential development

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of oral changes in relation to the natural history of the disease. Important aims will be to develop early diagnostic or predictive markers and to provide treatments and counselling for affected individuals. Treatment strategies can make use of earlier NIDR discoveries that monocytes are damaged by the AIDS virus and may even harbor the virus. They are not killed by the virus, however. Thus researchers will seek ways to eliminate the virus and restore the immune capacity of the cells.

Additional research plans include tracking when and in what quantities the AIDS virus appears in oral fluids; noting what changes may occur in the oral flora in the course of development of AIDS, and what microorganisms may be associated with opportunistic infections or malignancies. Other research will include studies of the invasiveness of Kaposi sarcoma cells and a focus on aberrant changes in another class of immune cells, the B lymphocytes. Clinical studies will include research and treatment for chronic pain experienced by some AIDS patients which is associated with nervous system damage.

The ability of the Institute to respond quickly to a sudden health emergency such as AIDS reflects the solid core of talent in the basic and clinical disciplines represented by NIDR intramural and extramural scientists. In our Long-Range Plan we foresaw the need to ensure that we maintain that base as well as build even closer ties between basic research and the clinical sciences in dentistry. Accordingly, the NIDR has developed a unique career development program--the Dentist-Scientist Award--designed for individuals with the DDS or DMD degree who wish to pursue careers in research. The 5-year program has been very warmly received by the research community and by year's end we expect to have 52 candidates enrolled in individual and institutional award programs, as well as in a comparable Physician-Scientist Award program.

Toward the same goal of enriching the talent pool and facilitating research advances, the NIDR has employed center grants, establishing 5 Dental Research Institutes some 20 years ago, and later, creating categorical research centers. In response to a request from the Committee the NIDR has now reviewed its use of these large grant mechanisms and reported its plans to Congress. This review engaged a broad segment of the dental community, led by a 20-member advisory panel representing the major professional organizations and NIDR advisory bodies. The NIDR is in agreement with the recommendations of the panel which, in essence, advise the Institute to use all existing NIH funding mechanisms, ranging from individual investigator-initiated grants to program projects and both categorical and non-categorical center grants; to strive for balance in the research portfolio, and to ensure that all large grants are awarded through open competition and rigorous peer review. Accordingly, the NIDR has now issued a request for applications for new Research Centers in Oral Biology (RCOBs), where multidisciplinary teams can address a variety of research issues. The first awards in this program will be made in FY 1987.

Periodontal disease research is benefiting from a concentrated study of relatively rare diseases that affect young people: juvenile periodontitis and prepubertal periodontitis. Both diseases appear to involve specific inherited defects in a critical host defense cell, the polymorphonuclear (PMN) white blood cell.

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These studies have given rise to a 5 site collaborative clinical study to elucidate the mode of inheritance as well as research aimed at identifying individuals at risk.

Commercial interest and involvement in preventing periodontal diseases through the use of antibacterial mouth rinses and other oral hygiene products is mounting. Some of these products are awaiting approved by Federal regulatory agencies for prescription use and should be available imminently. The new agents will be of considerable value in reducing accumulations of bacterial plaque above the gumline and hence in preventing and treating gingivitis. Since more advanced cases of periodontal disease are preceded by gingivitis, prevention of gingivitis may significantly reduce the incidence of advanced periodontal disease.

The NIDR remains committed to achieving even greater reductions in dental caries than have already been observed. We have commented that the emphasis must now be put on tailoring prevention and treatment to individuals at risk of developing decay, such as handicapped or immunocompromised patients. The NIDR plans a 1987 follow-up of its nationwide survey of school children conducted in 1979-80 to determine if caries reductions are being maintained.

Other important areas of caries research concern root caries, a form of decay that affects the exposed roots of teeth, a problem associated with gum recession in older individuals. The NIDR has been concerned about the extent and severity of this problem as well as the prevalence of secondary caries (decay around existing restorations) and of the periodontal diseases in adults and in the elderly. These concerns led the NIDR to undertake a survey of 20,000 adults and of the elderly last year. The examinations have now been completed and by the end of this year we expect to have the data in hand that will give us a significant baseline by which to judge the oral health status of working adults and non-institutionalized elderly.

This information is vital to the NIDR as it turns toward the challenge of preserving the human dentition for a lifetime. We have combined forces with the National Institute on Aging and the Veterans Administration to define a Research Agenda on Oral Health in the Elderly. That agenda will form the basis for joint research projects and announcements to the research community and to the public of our interest in fostering research in the area. One aspect that we are highlighting is the need for research on methods of oral health promotion and disease prevention appropriate for older groups.

Prevention is just not for children any more. Substantial reductions in the oral health problems seen in aging can be achieved by adopting a lifelong program of prevention. Ideally one begins in infancy, but those who start later in life, even at 50 plus, can reap enormous benefits from preventive regimens. Dental research has established that prevention works. Adults can and should act now to secure the healthy future they desire and deserve.

The budget request for FY 1987 is $96,482,000. I will be happy to answer any questions.

LÖE, DR. HARALD
Director, National Institute of Dental Research

July 19, 1926, Steinkjer, Norway

Education: Oslo University, Norway, D.D.S., 1952; Dr. Odont, 1961.

Professional History: 1952-1955, Instructor in Operative Dentistry, School of Dentistry, Oslo University, Oslo. 1956-1962, Research Associate, Norwegian Institute for Dental Research, Oslo. 1957-1958, Fulbright Research Fellow and Research Associate, Department of Oral Pathology, University of Illinois, Chicago. 1959-1962, University Research Fellow, Oslo University, Oslo. 1960-1962, Associate Professor, Department of Periodontology, School of Dentistry, Oslo University, Oslo. 1966-1967, Visiting Professor of Periodontics, Hebrew University, Jerusalem. 1962-1972, Professor of Dentistry and Chairman, Department of Periodontology, Royal Dental College, Aarhus. 1971-1972, Associate Dean and Dean-elect, Royal Dental College, Aarhus. 1972-1974, Professor of Dentistry and Director of the Dental Research Institute, University of Michigan, Ann Arbor. 1974-1982, Dean and Professor of Periodontology, School of Dental Medicine, University of Connecticut, Farmington.

Professional Organizations: American Dental Association; American Association for the Advancement of Science; International Association for Dental Research, American Association for Dental Research; American Academy of Periodontology; Commission on Oral Health Research and Epidemiology, Federation Dentaire Internationale; World Health Organization's Oral Research Advisory Group; American College of Dentists, International Association for Dental Research Periodontal Research Group; American Association for Dental Research Periodontal Research Chapter; International College of Dentists; Danish Dental Association; Scandinavian Association for Dental Research; Sigma Xi, The Scientific Research Society.

Honors, Awards: honorary doctorate degrees from the University of Gothenburg, Sweden, 1973; the Royal Dental College, Denmark, 1980; University of Athens, Greece, 1980; the Catholic University of Leuven, Belgium, 1980; Georgetown University School of Dentistry, Washington, 1983; the University of Lund, Sweden, 1983; and the University of Bergen, Norway, 1985; Alfred C. Fones Medal for Outstanding Achievement in the Service of Humanity, 1984; International Award of the Friends of the University of Connecticut School of Dental Medicine, 1983; Lister Hill Memorial Lecturer, University of Alabama, 1983; Daniel F. Lynch Award, Dental Society of Greater Waterbury, 1983; International Lecturer of the Year Award, Academy of International Dental Studies, 1983; Gold Medal, University of Ghent, 1982; Centennial Award, University of California School of Dentistry, 1982; Award of Merit, Hartford Dental Society, 1982; Irving Glickman Memorial Lecture, Tufts University, 1979; William J. Gies Award, American Academy of Periodontology, 1978; Arthur Merritt Memorial Lecturer, Baylor University, 1977; Certificate of Achievement, Connecticut Society of Periodontists, 1976; Massachusetts Dental Society International Award, 1973; honored by Her Majesty the Queen of Denmark (Knight of Danebrog), 1972; American Society of Preventive Dentistry International Award, 1972; International Association for Dental Research Award for Basic Research in Periodontics, 1969; Aalborg Dental Society Prize of Honour, 1969; Erik Berg Foundation Prize of Honor, 1965; Ingv. Stokke Prize for Outstanding Dental Research, 1959; Norwegian Dental Association 75th Anniversary Prize, 1959; honorary memberships in several professional societies.

Mr. **Natcher**. I am glad that you mentioned the award to Dr. Notkins. You know, at the Howard Hughes Institute ceremony that Mr. Neil and I attended on behalf of our Subcommittee, I made the statement at that time that one of the nice things about this Subcommittee is to have you people appear and talk with us about all of these matters concerning health and human services and the amounts contained in this bill. That is one of the nice parts about my assignment in this particular capacity; I get to talk with you people and hear you. It is of great benefit to us.

I certainly want to thank you for calling this to the attention of the Committee. This is the way it should be, Dr. Löe. A lot of you people are able people, dedicated people. You take this gentleman here that has just won this award; he could do a lot more financially, probably, at some other place, there is no question about that. But that is what makes us the greatest country in the world, Dr. Löe.

REDUCTION IN DECAY

Now, Dr. Löe, we understand that there has been a 50-percent reduction in the incidence of tooth decay in the American population. Are these statistics accurate, do you believe?

Dr. **Löe**. Yes, they reflect the improvement in dental health in the younger population. The data that you refer to, Mr. Chairman, came out of a survey made by the National Institute of Dental Research during 1979 and 1980.

The survey clearly showed that the drop in decay in the course of the last ten years has been quite dramatic. More than that, one-third of children below age 17 are caries free: they have never had a filling; never had a cavity. Now it is seven or eight years ago since that study was made. I have had a chance to see some data from California where in the past year two counties conducted surveys of children between kindergarten and the sixth grade. The studies show that we are holding the level of decline, possibly improving it. But the important finding was that the large majority of school children up to sixth grade are totally without tooth decay.

Another implication of these findings is that treatment needs among children have dropped to a very different level. In 1980 we found that 63 percent of the children did not need any dental treatment at all. We have also found that when it comes to tooth decay, there are no socioeconomic differences. Blacks show reductions in tooth decay; indeed most minority groups that have been studied show similar levels of reduction.

However, there is a difference between black and white children in terms of the need for treatment. Black children with tooth decay do not appear to get the dental treatment they need.

Finally, Mr. Chairman, it appears that a small percentage of children account for a high percentage of the decay found. It will be very important to try to identify these high-risk groups. Thus, one of our priorities is to develop methods by which we can predict which individuals in the child population are more susceptible to tooth decay than others.

WATER FLUORIDATION

Mr. NATCHER. Dr. Löe, how important has the fluoridation of community water supplies been in bringing about the reduction in tooth decay?

Dr. LÖE. Mr. Chairman, there is no doubt that the water fluoridation programs that were established back in the 1940's and continued in the 1950's and 1960's have had a major impact on dental health in this country. This is one of the reasons the United States stands out in the world today in terms of the dental health of the younger generation.

There are now 123 million people served by community water fluoridation programs—approximately 53 percent of the population. I might add that water fluoridation is a unique method of prevention that reaches beyond socioeconomic borders. The tap water coming into houses in communities where fluoridation is established reaches everyone, rich and poor. So it is a uniquely equitable and cost-effective measure of disease prevention.

FUTURE HEALTH IMPROVEMENTS

Mr. NATCHER. Do you expect that we will see similar improvements in dental health in the next 20 years?

Dr. LÖE. Since the early water fluoridation programs there have been increases in other vehicles for applying fluorides to the teeth, such as mouth rinses, tablets, dentifrices, and gels. Dental sealants have also been developed to prevent decay on the rough surfaces of teeth. All of these advances can be expected to have an impact in the future. I think that by the turn of the century, when the younger generations have moved up into adult life, tooth decay will be a disease that is pretty much under control.

FLUOROSIS

Mr. NATCHER. Dr. Löe, how much risk is there that excessive fluoridation will cause fluorosis or other conditions?

Dr. LÖE. Well, as a matter of fact, fluorosis has been with us all the time. So-called white spots on the teeth—and sometimes brown spots—were the clues that led investigators to the discovery of the beneficial effects of fluoride. Clinicians noticed that teeth with fluorosis had less tooth decay than teeth with no signs of fluorosis.

There are areas in this country where there are moderately high amounts of fluoride in the natural water supply, and in those areas, we continue to see fluorosis. As far as I know, this appears to be a cosmetic problem. We have no reason to believe that a health problem exists in these naturally high fluoride areas.

There has been some anecdotal information concerning the use of dentifrices and other fluoride measures in areas where the water is already fluoridated. We made a study a few years ago in areas in Illinois where fluoridation was started back in the fifties, to see to what extent other uses of fluoride had had an impact above that of water fluoridation. We found no essential changes in either the prevalence or the severity of fluorosis.

I might add, Mr. Chairman, that there are studies in Finland that show that an optimum fluoride level in the water supply may help in the prevention of osteoporosis. In terms of the benefits and risks of fluoridation, we feel that in the United States we are still very much on the positive side of the health factor. At this time and with optimum level of fluoride in the water and in other vehicles, we do not feel that we have a health problem at all.

DENTAL FEAR

Mr. NATCHER. Dr. Löe, the dentist that I go to is a skilled practitioner. He is a man that knows what he is doing. He has a cartoon hanging right beside his chair. It is about a 20-inch cartoon. A man is in the chair and the dentist is standing there with the drill and the man is shaking all over. And he says, "Mr. Brown, you seem to be a little nervous." Now, it is placed in a good position where you can see it. I look at it every time I get in that chair, Doctor.

Some people are afraid to go to a dentist, and you know it. How serious is this problem? And if you will, Dr. Löe, tell us what you are doing about it. I believe that you have a little research that you are supporting along this line. Is that correct?

Dr. LÖE. That is right, Mr. Chairman.

Mr. NATCHER. Why is that, Dr. Löe?

Dr. LÖE. I have not seen the cartoon in question and I am not sure I agree in putting such a thing up in a dental office.

Mr. HOYER. Not the proper atmosphere.

Dr. LÖE. I think there has been an enormous change in both the actual and the perceived pain in visiting the dental offices.

When I grew up, it was an essential pain experience to go to the dentist. Today, most patients who go to the dentist have no pain, and many, many of them do not even fear pain when going to the dentist.

So we are seeing a great improvement here. On the other hand, we have data to suggest that between 6 and 16 percent of Americans do not see the dentist because of fear of pain. That is an unfortunate misperception. The improvements in anesthetics and in other non-pharmacological ways of controlling pain and the fear of pain have brought us to the point where a dental experience is literally painless.

The dental research community has been very much involved in the development of methods of pain control for over a century. The development of nitrous oxide as the first anesthetic approach to pain control in the history of medicine came about as a result of discovery by a dentist, Horace Wells of Hartford, Connecticut, and also Dr. William Morton in Boston during the 1840's. Since that time, there has been a steady development of new substances and new methodologies for controlling pain, and dental research scientists continue to be leaders in the field. We have within our own Intramural Program a Pain Research Unit in the N.I.H. Clinical Center where we do research on a variety of acute and chronic pain conditions relating to all diseases—not only those that affect the face and the mouth and the head and the neck, but anywhere in the body.

These efforts are documentating numerous pathways in the nervous system important in the perception and response to pain stimuli. Today we know much more about the nerve tissues and transmitters involved in pain modulation and control.

We are testing new drugs and drug combinations for the control of pain; we have also explored behavorial factors and methods to relieve pain and anxiety. I repeat, dental investigators have been, and remain at the forefront of pain research, and we are proud of what has been accomplished in the course of these many years.

Mr. NATCHER. Thank you.

Mr. Conte, I yield to you.

WIDE-RANGING RESEARCH

Mr. CONTE. Thank you, Mr. Chairman.

Doctor, just reading your statement tells a lot about the wide range of important research conducted by your institute. It is not just the usual dental and oral diseases. It is AIDS, it is herpes, it is bone diseases, research on pain that you have just mentioned and many others. We are pleased to have you again before this Committee, and I want you to know that I think you are doing a great job down there.

Dr. LÖE. Thank you very much, Mr. Conte.

AIDS RESEARCH

Mr. CONTE. Your budget shows a four-fold increase for AIDS research. What current projects will you be expanding under this request, and what new areas do you hope to explore?

Dr. LÖE. Our support for AIDS research in 1985 was about $95,000. This was increased in '86 to approximately $600,000, and we expect to use $2,700,000 in 1987.

Over the past four or five years—since AIDS was first reported—we have gotten more and more involved in the AIDS research for a very good reason: The mouth is very much a part of the natural history of this disease. It is generally accepted that transmission of the disease is not primarily through saliva or fluids in the mouth. However, there are other aspects of AIDS that relate to oral tissues and fluids.

Kaposi's sarcoma occurs in approximately 25 percent of all AIDS patients. It is likely to be seen first in the mouth before anywhere else. There are also special changes in the oral mucosal tissues, seen in AIDS patients, so-called leukoplakias that develop early in some patients.

But probably the most important aspect of AIDS in the context of the total health of these patients is the effect of the destruction of the immune system on the oral cavity. All the microorganisms normally present in the mouth have a free ride. They grow in numbers and contribute to the pathology of the mouth.

The uncontrolled growth of bacteria in the mouth of AIDS patients creates special problems, so does the proliferation of mold and fungal organisms. These organisms may then contribute to the respiratory problems many patients later develop. The mouth is the entrance to both the respiratory and the gastrointestinal area, and any pathology that develops there earlier may lead to involvement of the other tracts later on.

So we are involved in both the natural history of AIDS, as well as in the treatment of patients. We are as well contributing to an understanding of the immunological deficits of the disease, along with the National Cancer Institute and the National Institute of Allergy and Infectious Diseases.

Mr. CONTE. Is it contagious with all this bacteria in the mouth?

Dr. LÖE. If by "it" you mean the AIDS virus, we follow the generally accepted position that AIDS is primarily transmitted through blood and intimate sexual contact. Bacterial infections in the mouth however can be transmitted from one person to the other. There is no question about that. That is an old observation and a particularly important one in spreading the microorganisms that we think are responsible for tooth decay. They can be transmitted from mother to child, for instance. There are several other examples of microorganisms that can be transmitted from one individual to the other through mouth contact or other means.

You may be interested in knowing that you, Mr. Conte, and I, and everybody in this room, normally harbors something like 150 different species of bacteria in our mouths at any time. Most of them are innocuous; some of them are not. The harmful ones are responsible for most of the oral diseases that we study.

Mr. CONTE. I know a lot of people are alarmed over the discovery of AIDS antibodies in the saliva. What is your opinion on the risk this poses to the general public? Recently I read a story about two nurses that performed mouth-to-mouth on a person with AIDS, but no transmission of the disease was discovered. Does this tell us something? Is there still the possibility of——

Dr. LÖE. Well, the data that we have seen during the last three to four years suggests that transmission of AIDS through oral fluids or by mouth contact is not the major route of transmission of AIDS.

Mr. CONTE. Is what?

Dr. LÖE. Is not a major way of contracting the disease. However, some data show the presence of the AIDS virus in the mouth of some AIDS patients. Now, whether the virus comes into the mouth from the secretion of saliva, from the bloodstream or other oral fluids are questions that remain to be answered. In this regard, we are investigating the possibility that saliva may be contaminated by blood components that enter into the mouth through periodontal disease or other lesions in the mucosal lining of the mouth.

But whether that represents the only mode of entry of the virus into the mouth, we do not know at the moment.

Mr. CONTE. Certainly there would not be any doubt about contact if a person is affected with AIDS in the mouth if the dentist, say, had a cut on his finger and got it into his bloodstream. There would be no doubt about that.

Dr. LÖE. Well, I do not think it is necessarily a fait accompli either. There has to be a certain quantity of virus transmitted to cause disease. If one does not have that level or critical mass, a disease need not result.

So far no dentist in the country has been contaminated with the virus through patient contact and that is a reassuring thing.

Mr. CONTE. How about in reverse? How about the dentist who has AIDS and works in the mouth of an individual?

Dr. Löe. We recommend that dentists with AIDS not see patients. This is because the nature of dental treatment involves exposure of practitioner and patient to blood, saliva and oral fluids. I might add, however, that we have had no indication that any dentist in this country has transmitted the disease to a patient.

HERPES VACCINE

Mr. Conte. Doctor, over the years I have followed with you the development of a herpes vaccine. Your statement gives some encouragement on this. What is the present status of that vaccine, and what kind of effectiveness is it showing both with herpes I and herpes II virus?

Dr. Löe. As I reported last year, research in our Intramural Program led to the development of a recombinant vaccine using a protein on the surface of the herpes virus as an antigen to increase antibodies in mice. The antibody production in the vaccinated mice protected against lethal challenges of herpes virus.

I also reported that the mice were protected against both Type I and Type II.

Now, one year later, we have evidence to show that the mice that were immunized last year are still protected against lethal doses.

That is an important observation because it is the first time we have had an opportunity to assess the duration of effectiveness of a recombinant vaccine.

We also have been supporting a grantee who has been studying the protein used in the recombinant vaccine. He has identified a chain of a few amino acids—a peptide—that could serve as the antigen instead of the whole protein.

The importance of that work is that it might be possible to synthesize this peptide and use it alone, without having to introduce the antigen into another vehicle like the vaccinia virus, for instance, that was used in the recombinant vaccine. Animal tests will continue in both the intramural and extramural investigations over the next year or two, and eventually we should be able to move on to human trials.

Mr. Conte. Thank you, Mr. Chairman.

Mr. Natcher. Mr. Hoyer.

DENTIST SCIENTIST AWARD

Mr. Hoyer. Thank you, Mr. Chairman.

Doctor, as you know, I am very interested in the Dentist Scientist Award Program. The Chairman has been very kind to include a million-and-a-half dollars in addition to your request, along with the ranking member, Mr. Conte and the rest of the Committee. It has been an add-on. We did that, as you know, in 1985. We did it again this year. Presumably that one and a half million was cut by 4.3 percent—I say presumably. Was it? Because I am not sure it is a PPA. It is a PPA, okay.

Now, I looked for it in the '87 budget. Is it there? Is there a——

Dr. Löe. There is no increase in the Dentist Scientist Award program for 1987.

Mr. Hoyer. Okay. But the one-five——

Dr. LÖE. We essentially are staying level with the '86.

Mr. HOYER. All right. Fine.

Now, let me ask you something. There were a total of 25 in '85; I presume there are going to be an additional 25 in '86?

Dr. LÖE. We hope that by the end of this fiscal year we will have 52 people in the program.

Mr. HOYER. Doctor, in light of your interest which you mention on Page 5 of your statement, I think this is an important initiative on your part and I am pleased to support it very strongly. Are we coming anywhere close to what would be an optimum, or at least even an adequate level of support? I realize that we are not going to come to the optimum level in the fiscal times we are in.

My question is: Could we do better? Could we do more? And if we had more money, do we have the need out there?

Dr. LÖE. Well, as you remember from our discussion last year, we had a program planned for the Dentist Scientist Award that would take us to 150 students in the program by 1989.

Mr. HOYER. So we are a third of the way.

Dr. LÖE. That plan assumed that we would feed into the program 25 candidates every year as we went along, and that by 1989 we would start to graduate people from the program and that the next four years would turn out approximately 150 dentist scientists.

Mr. HOYER. Consistent with that objective, what do I need to do, assuming the Committee would agree that that is a worthwhile objective this year?

Dr. LÖE. Mr. Hoyer, I would be reluctant to tell you what you should do. I must say, however, that if we were to follow that plan, we would need an additional one-and-a-half to two million dollars per year in order to sustain that momentum that we have defined.

As it stands, we would not be able to add anyone during 1987, and, of course, we have no notion of what will happen beyond that.

Mr. HOYER. Doctor, would it be a proper observation of mine that that would be a priority item? I do not necessarily mean that you would make it number one on a list of ten, but would you include it as a priority item?

Dr. LÖE. It has been one of our priorities over the last years along with some other. It is not the only priority that we have.

Mr. HOYER. I understand that. I was not asking you to choose. I would not be justified in doing it. I know you would not tell me what to do and I appreciate that sensitivity, but if I did it I would want to know that I was moving on a priority item. That is what I am saying.

Dr. LÖE. I would like to add, Mr. Hoyer, that the National Academy of Sciences has completed a study of the need for biomedical research and behavioral research scientists in the future, the immediate future, and have made a very special recommendation in their report of increasing the number of clinical scholars and clinical scientists in dental research, where they feel that we have been underpopulated and that we need to shore up the research training programs.

So this would be in line with their recommendation.

PRIVATE SECTOR COLLABORATION

Mr. **Hoyer**. Thank you.

Doctor, assuming as we all know and we have heard both from NIH and others, that we face limited budgets, at least for the short term, is your institute doing anything to investigate the potential for better collaboration and utilization of the private sector? And if so, what is being done, sir?

Dr. **Löe**. Yes. I think both for budget reasons and for other reasons we have sought to involve private industry as it relates to our mission. We have always had a good working relationship with some of the drug companies and some of the dental materials companies. More recently, we have seen the growth of biotechnology companies where we are also developing working relationships, in bone and connective tissue research, for example. In general, these relationships have been on the personal level of scientist to scientist.

In the past few weeks we have completed an agenda for a meeting that we will have in May. We plan to invite major companies that relate to dental research for a conference on the NIH campus. We expect to have at least 60 companies represented. We plan to demonstrate to them what the Dental Institute has accomplished in molecular biology, in clinical research, and in materials science research, and see to what extent we can make linkages with the research components within the corporations. These could remain at the scientist to scientist level, but more formal institute-to-corporation relationships might also develop.

SAVINGS FROM RESEARCH

Mr. **Hoyer**. Thank you very much, Doctor. I continue to be impressed with the presentations you make before the Committee, particularly as it relates to the progress that we have made and as it relates to the savings that have been effected by that progress. I did not know the specific figure in this year's testimony; I know we discussed it last year.

Dr. **Löe**. Right.

Mr. **Hoyer**. And I have discussed it with Dr. Wyngaarden, because I think that is one of the best arguments we have for spending money in this area; not only is it advantageous to the health of our citizens, but it is also, from an economic standpoint, a good investment in that it is a substantial savings on obviously a one-to-five or one-to-ten ratio of expenditures to savings. I congratulate you and your institute on the work that you are doing, sir.

Thank you very much.

Dr. **Löe**. Thank you very much.

Mr. **Hoyer**. Thank you, Mr. Chairman.

CENTERS

Mr. **Natcher**. Now, Dr. Löe, you have provided the Committee with a report on dental research centers. We will insert the report in the record at this point.

[Information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of Dental Research

FINAL REPORT

Use of the Center and Related Large Grant Mechanisms of Support in Meeting the Nation's Dental Research Needs

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October 1985

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of Dental Research

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Use of the Center and Related Large Grant Mechanisms of Support in Meeting the Nation's Dental Research Needs

EXECUTIVE SUMMARY

In House Report No. 98-911, the Committee on Appropriations requested that a report be prepared and submitted on the National Institute of Dental Research's planned use of the center grant support mechanism. The Institute was asked to seek broad consultation within the dental research community in developing its plans and to address the issue of opening competition for these awards. The following is submitted in response to that request.

A broadly representative ad hoc Consultant Panel was appointed by the NIDR Director to assist the Institute in developing this plan. In the course of its study, the Panel informed the dental research community of its activities and solicited input by mail and through a series of open hearings.

The Panel's final report was reviewed by the National Advisory Dental Research Council who recommended its implementation. A subcommittee of the Council worked with NIDR staff in developing the implementation plan described in this report to Congress. This plan has been reviewed and approved by the full Council.

The NIDR plans to continue to use the P50 center grant mechanism to support both specialized categorical/thematic research centers and the type and scope of research that has been supported under the Dental Research Institutes and Centers (DRIC) program. All qualified institutions will be eligible to submit applications in response to the NIDR-issued request for applications and to compete competitively for available resources. All large grants will undergo uniformly rigorous merit peer review and only projects of the highest quality will be funded. To further ensure open competition, grants supporting similar research areas will have common starting and termination dates.

The NIDR plans to expand its existing program of investigator-initiated P01 program project grants. Additionally, the NIDR plans to utilize for the first time the P30 core grant mechanism to support shared resources for investigators receiving R01 and P01 support. Core grants will be of particular assistance to those institutions making concerted efforts to strengthen their interdisciplinary research capability.

Use of the Center and Related Large Grant Mechanisms of Support in Meeting the Nation's Dental Research Needs

FINAL REPORT

I. INTRODUCTION

In considering the National Institute of Dental Research (NIDR) Fiscal year 1985 budget, the House of Representatives Committee on Appropriations stated:

> "The Committee expects that the Institute (NIDR) will continue to develop plans for open competition for the funds that become available after FY 1985 as the existing Institutes (the five Dental Research Institutes and Centers, DRIC's) reach the end of their approved grant periods. The Committee urges that these planning efforts take into consideration achievements of the existing Institutes (DRIC's) and include broad consultation within the dental research community regarding the continued need for this kind of program. The Committee requests a special report, to supplement the 1986 budget request, on the Institute's (NIDR's) plans for opening up the competition for institutes and centers awards as well as plans for funding new types of centers." (House Report No. 98-911, page 42, with clarifications inserted in parentheses)

This directive was prompted by the NIDR's proposed phase-out of support for the Dental Research Institutes and Centers program over a 4-year period. In its place, the NIDR had planned to implement an expanded program of categorical and thematic centers.

II. BROAD CONSULTATION PROCESS AND OUTCOME

In response to the request of the House Committee on Appropriations, the NIDR Director appointed, in November 1984, a broadly representative 20-member ad hoc Consultant Panel to assist the Institute in this planning effort and to ensure broad consultation with the dental research community. This Panel consisted of three members from the National Advisory Dental Research Council, two from the NIDR Programs Advisory Committee, two from the NIDR Long-Range Research Plan Coordinating Committee, one from the NIDR Special Grants Research Review Committee, one from the NIH Oral Biology and Medicine Study Section, all five Dental Research Institute and Center (DRIC) directors, directors of three of the specialized centers supported by the NIDR, one member nominated by the American Association for Dental Research, one member nominated by the American Dental Association, and one member nominated by the American Association of Dental Schools. The Panel was chaired by a member of the National Advisory Dental Research Council.

The appended final report of the ad hoc Consultant Panel identifies each member of the Panel and provides a detailed description of the Panel's activities and conclusions. In carrying out its charge, the Panel reviewed the history and current usage of the grant support mechanism for institutes, centers, and program projects used by the NIDR and other NIH institutes. Information-gathering efforts included not only a special hearing at which representatives from all the NIDR-supported Dental Research Institutes and Centers, specialized centers, and program projects were invited to participate, but also a series of open hearings at which input was solicited from the dental research community at large. It is estimated that nearly 800 individuals and organizations representing all segments of the dental research community were involved in the broad consultation process. On the basis of the information generated over a 5-month period, the Panel developed the following nine recommendations. The rationale for each of these recommendations is discussed more fully in the appended final report of the Panel.

Recommendation 1: Full Range of Research and Support Mechanisms

The Panel recommends that the NIDR support the full range of basic, applied, and clinical research activities through the large grant mechanisms and through the traditional investigator-initiated research grants.

Recommendation 2: Research Balance

The Panel recommends that the NIDR, in consultation with the scientific community, continue to strive for a balance between research needs and capabilities in supporting extramural research programs by identifying new and promising areas to the research community and by reducing emphasis on those areas in which there appears to be an overcommitment.

Recommendation 3: Open Competition

The Panel recommends that the NIDR utilize all practical approaches to ensure meaningful competition not only among the group of institutions currently supported by large grants but also by other institutions. To ensure maximum competition, the Panel recommends that the NIDR establish common starting and termination dates for similarly targeted work, that program announcements and RFA's for new and competitive renewals be released with the longest possible response times, and that competing and new applications be able to compete for the same budget ceiling.

Recommendation 4: Large Grant Review Procedures

The Panel recommends that the NIDR, through the National Advisory Dental Research Council, ensure that large grants reviewed by special study sections be funded on the basis of quality assessments equivalent to the initial reviews by the regular study sections of the NIH Division of Research Grants. It is suggested that the NIDR establish a core group of large grant reviewers who could be augmented by special review members on an ad hoc basis. Such a core review group should facilitate greater uniformity of reviews.

Recommendation 5: Centers and Large Grants

The Panel recommends that the NIDR continue to employ the P50 Center grant mechanism as well as other types of grant support for the noncategorical type of research that has been conducted by the DRIC's. The Panel reaffirms the continuing commitment and need for both multidisciplinary and multicategorical approaches and thematic and categorical approaches to basic and clinical dental research supported by large grant mechanisms.

Recommendation 6: Investigator-Initiated Large Grants

The Panel recommends that the NIDR expand its existing program of investigator-initiated program project (P01) grants.

Recommendation 7: Core Grants

The Panel recommends that the NIDR utilize the core grant (P30) mechanism to provide stable support for teams of qualified investigators who are currently being supported under the P01 and R01 grant mechanisms.

Recommendation 8: Demonstration Research Grants

The Panel recommends that the NIDR support demonstration research projects under the center grant mechanism.

Recommendation 9: Increase Budget and Number of Grants

The Panel recommends that the NIDR seek, through its planning and budget process, to increase the budget supporting large grants for dental research by $10 million and the number of grants supported under the center grant mechanisms by 22 grants.

III. NIDR PLANS FOR USE OF CENTER AND RELATED LARGE GRANT SUPPORT MECHANISMS

The ad hoc Consultant Panel's final report was presented to the NIDR Programs Advisory Committee and the National Advisory Dental Research Council (NADRC) for review and discussion at their spring meetings. Both advisory groups fully endorsed the report and recommended that the NIDR implement it to the degree possible. A special subcommittee of the NADRC was appointed to work with the NIDR staff to develop the implementation plan presented in this report, as well as to formulate a broad policy statement regarding use of the full range of large grant support mechanisms. The broad policy statement and this report were subsequently reviewed and endorsed by the full National Advisory Dental Research

Council. Additionally, a specific Request for Applications (RFA) announcing open competition for the P50 multidisciplinary centers program was approved by the National Advisory Dental Research Council at their September 1985 meeting and is pending issuance.

The NIDR has accepted the rationale presented by the ad hoc Consultant Panel. Specifically, the NIDR plans to continue to use its large grant program to provide support for the type and scope of research that has been conducted by the DRIC's. Further, the Institute has developed a plan to implement the Panel's recommendations, with one exception: The NIDR chooses to defer, at present, action on Panel Recommendation 8 which calls for the support of demonstration research projects under the center grant mechanism. It does so for two reasons. First, it is felt that available NIDR staff and financial resources should be initially concentrated on the implementation or refinement of the large grant program described below. Second, demonstration research projects are now being supported by the NIDR using other mechanisms, chiefly contracts. However, the NIDR will reassess the need to expand its large grant program to include demonstration research projects following enactment of the implementation plan for large grants. Finally, Recommendation 9 will be addressed by the NIDR through its regular planning and budgeting process and is not discussed in this report to Congress.

The NIDR will continue to give highest priority to the support of individual investigators by means of the traditional investigator-initiated competitive research (R01) grants. The NIDR also plans to utilize available large grant support mechanisms to carry out its mission as a national resource and focal point for the support of research and research training relevant to oral health and disease (Panel Recommendations 1,2,5-7). The NIDR believes that such large grant support is necessary to further the objective of bringing teams of investigators into effective collaborative relationships. From an applicant institution's point of view, large grant support should facilitate efforts to strengthen research environments by increasing interdisciplinary and multidisciplinary research capabilities. The NIDR plans to ensure open competition in all of its large grant support programs and to establish uniformly rigorous review procedures to support this open competition principle (Panel Recommendations 3 and 4).

A. Use of the P50 Research Center Grant Mechanism

1. History

The NIDR first used the P50 center grant program in the late 1960's when it initiated a program especially designed to strengthen the science base of dental research. Five dental research institutes and centers (DRIC's) at the Universities of Alabama, Michigan, North Carolina, Pennsylvania, and Washington were funded to implement multidisciplinary programs of research. Key features of the DRIC program were its utilization of the broad resources of the university, its ability to attract highly qualified scientists into dental research, and provision of a stimulating environment for training future dental researchers. Subsequent competition for these center awards was limited to the five institutions initially supported.

Starting in the mid 1970's, largely as a consequence of the strengthened base of biomedical research activity in dentistry and especially the expanded pool of competent investigators, NIDR's consultants and advisory groups recommended that the NIDR utilize the research center mechanism to focus on specific oral disease research areas. This recommendation was based on concerns that there had not been a sufficiently coordinated attack, combining basic and clinical research approaches, on the most important dental disease problems, specifically the periodontal diseases and dental caries. In FY 1985, the NIDR was supporting seven specialized categorical/thematic centers -- four periodontal disease research centers and three dental caries research centers -- utilizing the P50 center grant mechanism.

2. Action Plan

- In accord with Panel Recommendations 1 and 5, the NIDR will continue to utilize the P50 center grant mechanism to support both specialized categorical/thematic research centers and the multidisciplinary Dental Research Institutes and Centers type of center. The latter will be entitled Research Centers in Oral Biology (RCOB).

The full range of basic to clinical research will be supported under the center grant mechanism. The primary objectives will be to provide support for collaborative multidisciplinary attacks on specific disease entities or on basic research areas targeted by the NIDR as having high programmatic relevance. Center grant support will be provided for both research and shared core support services. Applications for all P50 center grants will be considered only in response to specific announcements of programmatic needs issued by the NIDR. Awards will be for a 5-year period and continuation of support beyond the initial project period will be possible only if the NIDR reissues a Request for Applications (RFA) and the applicant institution is successful in the resulting open competition. Decisions to issue or reissue specific RFA's will be made with the advice of the National Advisory Dental Research Council and other NIDR Advisory bodies. All RCOB center grants will have common start and termination dates, as will specialized categorical/thematic center grants focused on similar research areas. All applications will be rigorously peer reviewed and, through the use of a core set of reviewers, the uniformity of the review process will be ensured.

The NIDR plans to initiate the 5-year RCOB program in FY 1987, the same year that grant support for two existing DRIC's (at the Universities of Washington and North Carolina) will terminate. In order to provide necessary lead time to prepare applications, should these two institutions wish to apply for RCOB funds, as well as ensure that all other interested institutions have the necessary time to develop competitive applications, the NIDR plans to initiate an RFA as soon as possible. It is anticipated that all five currently supported DRIC's as well as other qualified institutions will develop applications in response to this RFA, since the NIDR plans to utilize this announcement as a means of establishing common starting and terminating dates, beginning in FY 1987, for the RCOB program. If any of the three existing DRIC's whose support expires after FY 1987 are not successful in this open competition (or if they choose not to enter this competition), support will continue until their current project period expires. All institutions, including the five existing DRIC's, will continue to be eligible to compete for specialized centers, program projects, individual research grants, and appropriate core support.

B. Use of the P01 Program Project Grant Mechanism

1. History

The P01 program project grant is a large grant support mechanism that has been utilized by the NIDR since 1962 to support broadly based multidisciplinary basic and applied research programs having a focus on a specific area of research, such as cleft lip and palate research. In FY 1985, the NIDR was supporting 10 program project grants.

Program projects differ from research supported under the P50 center mechanism in that they are investigator-initiated projects focused on a single major research area or unifying theme. In terms of funding, approved P01 grants compete directly, on the basis of scientific merit, with other investigator-initiated applications, most notably the traditional individual research project grants (R01's).

2. Action Plan

Within the limits of available resources, the NIDR, in accordance with Recommendations 1 and 6 of the Panel report, plans to expand its existing program of investigator-initiated P01 program project grants. This support mechanism has demonstrated great usefulness and flexibility by adding collaborative and multidisciplinary dimensions to the more traditional investigator-initiated R01 grant program.

Because they are investigator-initiated, program project applications can be developed at any time and submitted for the regular grant receipt dates. Five years of support may be requested and competitive renewal applications may be submitted. All applications for program projects will undergo uniformly rigorous peer review.

C. Future Use of the P30 Core Grant Mechanism

Recommendation 7 of the Panel report urges the NIDR to utilize the P30 core grant mechanism to support shared resources for investigators receiving P01 and R01 support in a particular institution. Although the NIDR has not previously used this grant mechanism, it concurs with the Panel that this type of support is currently needed. The availability of this support mechanism would facilitate those institutions making concerted efforts to strengthen substantially their interdisciplinary research capability.

The P30 core grant is appropriate when a substantial number of high-quality NIDR-funded grants exist at an institution. Here the need is for joint sharing of core support services such as laboratory and animal facilities, personnel, specialized equipment, and other types of research services and administrative assistance. The NIDR plans to draw upon the experience of other NIH institutes in developing its own core grant support program.

IV. CONCLUSIONS

This report, prepared in response to the request of the House Committee on Appropriations, describes the NIDR´s plans for its large grant programs and discusses plans for opening competition for the RCOB multidisciplinary research center program. It has been prepared following an extensive consultation process with the dental research community and hs been endorsed by the National Advisory Dental Research Council.

The NIDR believes that the broad consultation process, as reflected in the appended final report of the 20-member ad hoc Consultant Panel, has been extremely valuable. The NIDR is fully committed to implementing all the Panel´s recommendations with the exception, at present, of the recommendation for the support of demonstration research under the centers program. In particular, the NIDR accepts the advice of the dental research community and the recommendation of the Panel, and will continue to provide support under its future large grant program for the type and scope of research that has been conducted by the DRIC´s. Additionally, the NIDR concurs with the Panel´s recommendation that it begin to utilize the P30 core grant support mechanism. The implementation plans of the NIDR are designed to ensure full and open competition among all eligible individuals and institutions for support under the various large grant programs. The NIDR also will ensure that all large grant applications undergo uniformly rigorous merit review and that only projects of the highest quality are funded.

THE USE OF LARGE GRANT MECHANISMS IN MEETING THE NATION'S DENTAL RESEARCH NEEDS

FINAL REPORT OF THE NIDR AD HOC CONSULTANT PANEL ON CENTERS AND LARGE GRANTS, MAY 1985

May 15, 1985

Dr. Harald Löe
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Dear Dr. Löe:

The members of the Ad Hoc Consultant Panel on Centers and Large Grants are pleased to respond to your request to provide guidance on the future use of this NIDR centers and large grant program. Our enclosed final report is representative of our broad consultation with all interested members of the dental research community.

We agree that the five Dental Research Institutes and Centers have made major contributions to strengthen the science and manpower bases in oral health research. However, we also agree that other universities and institutions have developed significant research capabilities and that open competition by qualified institutions and investigators is fundamental to future achievements in dental research.

We recognize the need for stable support for qualified teams of investigators and a continuing commitment for noncategorical large grant research approaches. We also believe that it is important to move forward with the thematic or categorical center grant program. While recognizing the current limitation of funds, we urge the NIDR to seek through its planning and budget processes a substantial increase in the number of center grants as well as increased funding goals for other large grant mechanisms of support.

It is our hope and belief that the implementation of our recommendations included in this report will strengthen the potential for further achievements in the etiology, epidemiology, prevention, diagnosis, and treatment of oral diseases. We have welcomed this opportunity to provide our scientific and administrative advice to the National Institute of Dental Research.

Sincerely,

Robert J. Fitzgerald

Dr. Robert J. Fitzgerald
Chairman
NIDR Ad Hoc Consultant Panel on
Centers and Large Grants

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SYNOPSIS

The House Appropriations Committee, in its report on the FY 1985 budget, directed the National Institute of Dental Research (NIDR) to develop plans for the open competition and future use of center awards. The Committee urged that these planning efforts concerning the NIDR large grant program include broad consultation with the dental research community.

In response to the House Committee's direction, the NIDR Director appointed an Ad Hoc Consultant Panel of 20 members, broadly representing the dental research community. This Panel was asked to examine the issues and provide the NIDR with guidance in carrying out this planning task. Since December 1984, the Panel has reviewed the history, achievements, and current use of centers/large grants at the NIH and the NIDR. Senior administrators and program staff of the NIH, the NIDR, and three sister NIH Institutes provided background information. In addition, through specially scheduled forums and hearings, the Panel solicited verbal and written comments and suggestions from all principal investigators at NIDR's currently supported institutes, centers, and program project large grants; deans and other university administrators at every dental school in the United States and Canada; all active investigators supported by the NIDR; and all major dental organizations. It is estimated that nearly 800 individuals from the dental research community were involved in this activity.

The information received by the Panel was evaluated in the context of the NIDR long-range research plan, "Challenges for the Eighties." The Panel recognized the major importance of the individual investigator-initiated grant program and the contributions of the five original Dental Research Institutes and Centers (DRIC) to dental science. The Panel also noted the role of DRIC's in developing research strength at other universities and institutions. The Panel concluded that significant gains in the oral health and welfare of the public are possible through expanded use of competitive large grant/center programs that would be thematic or categorical in nature and by continued support for noncategorical basic research through the centers mechanism.

In brief, the Panel recommended that the Institute support basic, applied, and clinical research through the large grant mechanisms and through the traditional investigator-initiated research grants. Competition for these grants must be open to all qualified persons or institutions, and all applications must undergo uniformly rigorous peer review. The NIDR must strive for balance in its extramural program, taking into consideration research needs and capabilities. The NIDR should continue to employ the P50 center grant mechanism as well as other types of grant support for the noncategorical type of research that has been conducted by the DRIC's. At the same time, the NIDR, through its planning and budgeting process, should strive for a budget increase of $10 million to augment its large grant program and to increase the number of the NIDR-initiated center grants.

INTRODUCTION

The National Institute of Dental Research was established in 1948 with the broad mandate to improve the dental health of the people of the United States. By the mid-1960's, however, very little progress had been made in the control and prevention of major dental diseases. There were many reasons: the existing fund of basic knowledge was inadequate; few research training opportunities existed; and only a few trained investigators were working in the dental research field.

In response to these problems, the Dental Research Institutes and Centers Program was established. The program was designed to broaden and strengthen the scientific base that underlies the national capability to improve oral health. It not only sought to achieve the most from existing dental research capability but also to develop new research manpower by challenging scientists from medical, engineering, and graduate schools as well as other university components. In addition to this program, the NIDR strengthened and enlarged its research training programs. The Institute continued to encourage investigator-initiated research through the single investigator (R01) and program project (P01) grant mechanisms. It also further developed the research career development program. In more recent years, categorical or clinical research centers were established in the areas of dental caries and periodontal diseases.

These efforts succeeded in expanding the cadre of highly qualified investigators and in creating centers of excellence in dental research at several institutions. New concepts and technologies were developed, and these have begun to revolutionize the oral health field. As a result, the nature of dental practice is changing, and significant improvements in the Nation's oral health are being realized.

To help provide guidance and establish priorities, the NIDR developed a long-range research plan entitled "Challenges for the Eighties." In this document, existing knowledge has been summarized and evaluated, and directions have been identified for future research. As described in the long-range plan, exciting opportunities exist for capitalizing on past research investments as well as pursuing new fundamental and applied areas.

Recognizing the success of its programs, and on the basis of its own assessments and the advice of advisory bodies, the NIDR planned a change of direction. A decision was made to phase out support for the Dental Research Institutes and Centers Program over a 4-year period. Using funds made available by the phaseout plan, the NIDR proposed to implement an expanded program of thematic and categorical centers on a fully competitive basis. However, during the consideration of the NIDR fiscal year 1985 budget, the House Appropriations Committee directed the NIDR to undertake a special planning effort concerning the future use of institute and center/large grant awards:

> "The Committee expects that the Institute will continue to develop plans for open competition for the funds that become available after FY 1985 as the existing Institutes reach the end of their approved grant periods. The Committee urges that these planning efforts take into consideration achievements of the existing institutes and include broad consultation

> within the dental research community regarding the continued need for this kind of program. The Committee requests a special report, to supplement the 1986 budget request, on the Institute's plans for opening up the competition for institutes and centers awards as well as plans for funding new types of centers." (House Report Number 98-911, page 42)

The NIDR Ad Hoc Consultant Panel on Centers and Large Grants was appointed by the NIDR Director to assist in this planning effort and to ensure broad consultation with the dental research community. Members of this broadly representative 20-member Panel were selected from the following groups and organizations: three members from the National Advisory Dental Research Council, two from the NIDR Program Advisory Committee, two from the NIDR Long-Range Research Plan Coordinating Committee, one from the NIDR Special Grants Research Review Committee, one from the NIH Oral Biology and Medicine Study Section, all five directors of the NIDR-supported dental research institutes, directors of three of the specialized centers supported by the NIDR, one member nominated by the American Association for Dental Research, one member nominated by the American Dental Association, and one member nominated by the American Association of Dental Schools. The Panel was chaired by a member of the National Advisory Dental Research Council. Appendix A lists the members and their affiliations.

PANEL ACTIVITIES

To carry out its charge, the ad hoc Panel reviewed the history and assessed the current usage of support mechanisms for institutes, centers, and program projects by the NIDR and other NIH Institutes. At its initial meeting on December 6-7, 1984, the Panel met with the NIH Deputy Director for Extramural Research and Training who discussed the major issues relating to these funding mechanisms used by the NIH. Senior administrators from the National Heart, Lung, and Blood Institute, the National Institute of General Medical Sciences, and the National Eye Institute met with the Panel to describe the policies of their Institutes regarding funding for centers and institutes. These three Institutes were selected as representing the spectrum of usage of these funding mechanisms at the NIH. The NIDR staff also discussed the results of the several assessments of the centers and large grant programs that have been performed. These evaluations are summarized in appendix B.

The Panel learned that there were common characteristics between the various large grant mechanisms used at the NIH, primarily the specialized center mechanism (P50) and the investigator-initiated program project grant mechanism (P01). Therefore, it was decided to devote the second Panel meeting, held on January 24-25, 1985, to learning about these large grant programs. The Panel invited the principal investigators from the 5 noncategorical centers, 6 categorical centers, and 10 program project grants being supported by the NIDR to submit written comments and to attend the Panel's meeting to discuss issues concerning the strengths, weaknesses, suggested improvements, and future needs for their respective grant mechanisms. Twenty written reports were submitted, and 16 individuals appeared before the Panel.

Based on the information gathered, the Panel identified 10 major issues relating to its charge. These were summarized and used in the broad consultation phase of the assignment. Input was sought from the dental research community at large. The issue paper was distributed to approximately 150 dental school deans, associate deans for research, and other university administrators who attended a previously scheduled NIDR conference held in February 1985. Seven ad hoc Panel members who were in attendance accepted comments and suggestions.

Additional input from the research community was sought by mailing letters to all investigators currently receiving NIDR support. The Panel requested comments on the 10 major issues or any previously unidentified relevant issue. In addition to soliciting written input, the Panel held special hearings at the annual national meetings of the American Association of Dental Schools and the American Association for Dental Research. Both of these open hearings were held in March 1985 in Las Vegas, Nevada. Over 250 individuals from the dental research community participated.

As a result, the Panel is confident that every opportunity has been provided to all individuals and parties interested in participating in the process. A synopsis of the results of these efforts is included as appendix C.

The final meeting of the consultant Panel was held on April 1-2, 1985. The Panel considered all of the evidence, and particular attention was given to comments and suggestions generated during the broad consultation phase of the study. The Panel formulated its recommendations at this meeting and established a four-member subcommittee to coordinate the preparation of the final report.

RECOMMENDATIONS

The ad hoc Panel is cognizant that its charge was limited to formulating recommendations that would assist the NIDR in planning the future use of the large grant programs. However, the Panel states as a fundamental premise that the NIDR must continue to give highest priority to the support of the individual investigator by means of traditional investigator-initiated competitive research (R01) grants.

Having broadly considered the needs of the dental research community, the Panel submits the following recommendations and rationales to the Director of the NIDR.

Recommendation 1: Full Range of Research and Support Mechanisms

> The Panel recommends that the NIDR support the full range of basic, applied, and clinical research activities through the large grant mechanisms and through the traditional investigator-initiated research grants.

The Panel believes that there are special relationships between the NIDR and the dental research community that are different from most other NIH Institutes' relationships to their applicant communities. While dental researchers can seek support from other institutes, most oral health research is supported by the NIDR. The Panel believes that dental research will be served best by having the NIDR offer a variety of research support mechanisms and ensure that the full range of dental-related biomedical and behavioral research continues to be supported by the NIDR.

Recommendation 2: Research Balance

> The Panel recommends that the NIDR, in consultation with the scientific community, continue to strive for a balance between research needs and capabilities in supporting extramural research programs by identifying new and promising areas to the research community and by reducing emphasis on those areas in which there appears to be an overcommitment.

The Panel believes that the majority of research supported by the NIDR should be investigator generated. Nonetheless, it believes that the Institute, through its National Advisory Dental Research Council, has the responsibility for stimulating neglected areas of research, ensuring that promising findings are carried forward to application, and guarding against the concentration of limited resources in excessive, duplicative, albeit of high quality, research.

Recommendation 3: Open Competition

> The Panel recommends that the NIDR utilize all practical approaches to ensure meaningful competition not only among the group of institutions currently supported by large grants but also by other institutions. To ensure maximum competition, the Panel recommends that the NIDR establish common starting and termination dates for similarly targeted work, that program announcements and RFA's for new and competitive renewals be released with the longest possible response times, and that competing and new applications be able to compete for the same budget ceiling.

With specific regard to the funding for the five original DRIC's, the Panel recognizes that their establishment in the mid-1960's was intended to represent a phase in the development of dental research. Because of the then existing limited national dental research capability in the biomedical sciences and the objectives of the program to generate such a capacity, the Panel understands the NIDR's reasons for having maintained a long-term commitment to these five institutions by not allowing others to compete for this support. Because a number of other institutions subsequently have expanded their research capabilities in these basic areas of science, it is now incumbent upon the NIDR to ensure full and open competition among all capable institutions for all large grants supported by the NIDR.

In making the recommendation, however, the Panel recognizes that large grants involve teams of investigators and require significant commitments by their parent institutions. Therefore, should a large grant project be unsuccessful at the time of a competitive renewal or should the decision be made not to reissue an RFA in the given area that has been supported, attention must be given to providing the maximum lead time to allow an orderly conclusion of current research efforts.

Recommendation 4: Large Grant Review Procedures

> The Panel recommends that the NIDR, through the National Advisory Dental Research Council, ensure that large grants reviewed by special study sections be funded on the basis of quality assessments equivalent to the initial reviews by the regular study sections of the NIH Division of Research Grants. It is suggested that the NIDR establish a core group of large grant reviewers who could be augmented by special review members on an ad hoc basis. Such a core review group should facilitate greater uniformity of reviews.

The Panel strongly endorses the concept that similar research undergo equally rigorous merit review. While not citing any specific shortcoming, the Panel recognizes that large grants require review by teams of reviewers who are specifically selected on the basis of their expertise in the areas of science included within a given large grant application. Because of this selection process, merit assessment scores have the potential of differing from those that might be given by a regularly constituted study section that is responsible for the review of a broader range of science. In addition, the Panel found that this is a subject of concern within the dental research community and believes that it warrants special attention by the NIDR.

Recommendation 5: Centers and Large Grants

> The Panel recommends that the NIDR continue to employ the P50 center grant mechanism as well as other types of grant support for the noncategorical type of research that has been conducted by the DRIC's. The Panel reaffirms the continuing commitment and need for both multidisciplinary and multicategorical approaches and thematic and categorical approaches to basic and clinical dental research supported by large grant mechanisms.

In making this recommendation, the Panel acknowledges the expansion and maturation of dental research that has occurred since the DRIC program was initiated. Impressed by the achievements of large grant programs of support in dentistry, including the noncategorical and specialized centers supported by the NIDR, the Panel believes that the collaborative efforts of teams of investigators employing a variety of approaches to oral health problems present viable opportunities for continued advancement.

The Panel also reaffirms its support for the continued implementation and expansion of a program of thematic and categorical research supported under the center grant mechanism. To implement this recommendation, the Panel urges that program announcements or RFA's be structured to give qualified applicants the maximum opportunity to develop creative approaches to the research problem.

Consistent with its other recommendations, the Panel makes neither specific recommendations concerning the number of noncategorical DRIC-type grants that should be supported under the P50 mechanism nor any commitment to the five institutions currently being supported. Rather, by ensuring free and open competition and rigorous peer review, all eligible institutions will have equal access to compete for available funds.

The Panel recommends that in announcing the availability of such noncategorical grants, the NIDR incorporate to the extent possible the strengths of the provisions included in the original DRIC guidelines. These advantageous features include such items as the definite indication of university and/or institutional commitment for the establishment of a center and the requirements for internal review.

Conditions necessary for the NIDR to fully implement this recommendation are addressed in the Panel's final recommendation.

Recommendation 6: Investigator-Initiated Large Grants

> The Panel recommends that the NIDR expand its existing program of investigator-initiated program project (P01) grants.

The Panel was favorably impressed by the testimony that it received from representatives of current P01 grantees supported by the NIDR concerning the viability and efficiency of this grant mechanism and the many similarities in actual practice between this mechanism and the P50 center grant mechanism. In addition, the Panel was impressed by the testimony received from the broad research community urging continued reliance on the investigator-initiated approach to oral health research.

The Panel again calls attention to its fundamental premise and cautions that there should be no long-range adverse impact on the other investigator-initiated grant mechanisms, particularly the traditional research project grants. An expansion of the program project mechanism will require an increase in the number of new and competing NIDR research grants. The Panel therefore urges the NIDR to seek administration and congressional approval for increased funding of investigator-initiated research.

Recommendation 7: Core Grants

> The Panel recommends that the NIDR utilize the core grant (P30) mechanism to provide stable support for teams of qualified investigators who are currently being supported under the P01 and R01 grant mechanisms.

In the course of its activities, the Panel learned that other NIH Institutes use the P30 core grant mechanism to further their objective of bringing teams of independent investigators into collaborative relationships. In the Panel's opinion, the availability of this support mechanism would facilitate those institutions making concerted efforts to strengthen substantially their interdisciplinary research capabilities.

Conditions necessary for the NIDR to implement this recommendation are addressed in the Panel's final recommendation.

Recommendation 8: Demonstration Research Grants

> The Panel recommends that the NIDR support demonstration research projects under the center grant mechanism.

Based on ongoing research, the Panel believes that there are opportunities to improve the public's oral health through demonstrating and testing research in field settings in such areas as biomaterials, periodontal diseases, and caries. The Panel therefore urges the NIDR to support timely demonstration research projects either through separate grants funded under the center grant mechanism or by adding demonstration research projects to ongoing center grants.

Conditions necessary for the NIDR to implement this recommendation are addressed in the Panel's final recommendation.

Recommendation 9: Increase Budget and Number of Grants

> The Panel recommends that the NIDR seek, through its planning and budgeting process, to increase the budget supporting large grants for dental research by $10 million and the number of grants supported under the center grant mechanisms by 22 grants.

In support of this recommendation, the Panel urges that $3 million be immediately sought to fund the thematic and categorical centers that are either currently approved and awaiting funding or for which applications are being developed in response to NIDR-released RFA's. The Panel also urges that an additional $3 million be sought to expand the thematic and categorical centers program. The Panel further recommends that there be a minimum of 10 P30 core grants amounting to a total of $3 million based on the Panel's assessment of the existing pool of R01 and P01 investigators. Further, the Panel recommends that there be demonstration research grant add-ons to existing centers or freestanding demonstration research grants totaling at least $1 million to provide for the investigation of optimal methods of transmitting new knowledge into clinical practice. The Panel finds that the number of grants funded by the NIDR under the center grant mechanism must be tripled from the current level of 11 to carry out its recommendations.

CONCLUSIONS

In submitting its final report to the Director of the NIDR, the Panel is cognizant that the NIDR is confronted with the need to make immediate programmatic decisions. The Panel also recognizes that decisions concerning the NIDR large grant program cannot be delayed pending the availability of the recommended budgetary increases or an increase in the numbers of large grants. However, the Panel does urge that its recommended expansion be pursued aggressively.

The Panel does not elect to make recommendations affecting the managerial prerogatives of the NIDR. However, it does recommend that interim actions by the NIDR be consistent with the principles and intent of the Panel's recommendations.

The Panel concludes that the Nation's oral health research needs, as summarized in the NIDR long-range research plan, "Challenges for the Eighties," can be met best through a combined approach based on a foundation of individual investigator-initiated project grants augmented by a strong large grant program supporting centers of excellence.

In response to the question raised by the House Appropriations Committee, the Panel concludes that the NIDR should continue to use its large grant program to support the type of noncategorical research that has been conducted by the DRIC's as well as continue with the implementation of a program of thematic and categorical centers. It is essential that the necessary resources be made available. The NIDR must ensure that there is full and open competition in all research grant programs, including the large grant programs.

APPENDIX A

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APPENDIX B

OVERVIEW OF FORMAL EVALUATION-RELATED ACTIVITIES OF THE NIDR DENTAL RESEARCH INSTITUTES AND CENTERS (DRIC)

1972-1975 The efforts of the NIDR Working Group on DRIC Program Evaluation resulted in the establishment of several research questions (e.g., How valid are the DRIC's as an instrument for supporting research? What impact have the DRIC's had on dentistry? etc.), and evaluation methodologies were proposed.

1976-1981 Three NIDR formal research program evaluation studies were discussed since each included projects from the DRIC's that related to the categorical program being evaluated. These studies were of the Periodontal Disease Research Activity, National Caries Program, and Craniofacial Anomalies Research activities. The results of these evaluations were not analyzed according to the funding mechanism used.

1978 The Rand Corporation Study entitled "Comparison of Large Grant and Research Project Grants Awarded by the National Institutes of Health" was reviewed. Several findings specific to NIDR grants were presented. These findings showed that R01 and large grants were of comparable quality according to approval rates and priority scores. Differences were noted between these two types of grant holders in terms of journal and citation distributions of their publications. The R01 investigators published more in dentistry and clinical journals than in biochemistry and basic science journals. Whereas the large grant investigators published more in basic science and clinical journals than in dentistry journals. In addition, the large grant programs supported more interdisciplinary research and had a broader segment of the research community involved in their programs.

1980 A meeting of past and present Directors of DRIC's was convened to review program objectives and to establish evaluation criteria for the DRIC's.

1982 A Short-Term Descriptive Study of the NIDR DRIC's was described. Its purpose was to collect, synthesize, and analyze data available for program evaluation and management. A number of trends noted for all DRIC's (1974-1982) were described. These showed that the number of investigators with a D.D.S. declined; there was a decrease in the percent of full-time investigators; the number of collaborative projects increased; the NIDR funding of DRIC's in constant dollars decreased; the percent of funding provided by non-DRIC funds increased; and shifts occurred in program areas of research emphasis during this time period.

1984 Bibliometric Comparison of the NIDR's Centers Program with the Investigator-Initiated R01 Grant Mechanism. The findings of a bibliometric comparison of publications resulting from DRIC and R01 investigators were discussed. There were no differences in the number of papers published per year between the two groups. However, investigators that had both R01 support and participated in a center grant published about 50 percent more than investigators with only one type of support. Publications resulting from DRIC investigators appeared more in basic biochemistry journals, whereas R01 investigator papers tended to be in core dentistry journals. Adjusted for the subfield of publication, no differences were noted in the number of citations. The papers from DRIC investigators displayed more additional support sources and had a slightly greater number of coauthors (an indicator of collaboration) than papers by R01 investigators.

The overview ended with a discussion of the proposed plans for evaluating new centers as they become established.

APPENDIX C

INPUT FROM THE DENTAL RESEARCH COMMUNITY

To assist the NIDR in this planning effort, the Ad Hoc Consultant Panel initiated several information collection activities to obtain comments and suggestions concerning the center/large grant programs. These activities included:

- Letter to principal investigators of NIDR large grants.
- Letter to the dental research community requesting comments on large grant mechanisms.
- Forum at the NIDR meeting of dental school deans (February 5, 1985).
- Open hearing at the meeting of the American Association of Dental Schools (March 18, 1985).
- Open hearing at the annual session of the American Association for Dental Research (March 22, 1985).

These data collection activities provided for broad consultation with the dental research community in terms of numbers and scope of consultees. The methodology followed in each of these data collection activities is described below. This report summarizes the findings of the five information gathering efforts.

METHODOLOGY

Letters to Centers and Program/Project Principal Investigators

Letters were sent to the principal investigators of the 5 DRIC's, 6 NIDR-funded categorical centers, and 11 NIDR-supported P01 program project grants. These investigators represented every center program and program/project grant currently funded by the NIDR. The principal investigators were invited to submit written comments and appear at a Panel meeting to provide comments on the strengths and weaknesses and suggest improvements in their respective grant mechanisms. Principal investigators responded with written and verbal comments.

Letters to Dental Research Community

Over 700 letters were sent to the following groups in the dental research community:

- Deans of dental schools.
- Principal investigators of NIDR research grant awards.

- Presidents and executive directors of the:

  --American Association for Dental Research.
  --American Association of Dental Schools.
  --American Dental Association.

The letter included a background statement on the history and purpose of the Panel's activity and a list of general, open-ended questions developed by the Panel to elicit responses. Each recipient was asked to submit written comments on the questions to the executive secretary of the Panel.

Forum

During a conference sponsored by the NIDR to which the deans, associate deans, and other university administrators from every dental school in the United States and Canada were invited, a forum was convened regarding the NIDR's future use of centers/large research grants. The forum, attended by approximately 150 individuals, opened with an overview of the activities to follow and the events over the last year associated with the NIDR's plans to gradually phase down the support of the five DRIC's while implementing and expanding the thematic and categorical centers program. Attendees were informed of the pertinent sections of the House of Representatives Appropriations Committee report calling for the initiation of a planning effort and broad consultation within the dental research community. The purposes and activities of the Ad Hoc Consultant Panel on Centers/Large Grants were described, and the Panel members present were introduced. A handout was distributed to all attendees that provided background information concerning the Panel's activities and listed the 10 questions that were developed by the Panel to elicit useful suggestions from the dental research community. The meeting was then opened for comments from the floor.

Hearings

The hearings were conducted in the same manner as the forum with brief descriptions of the history and status of the planning and consultation activities related to the center/large grant programs. Over 200 individuals attended the two hearings. Panel members were introduced, and the hearings were opened for comments.

SUMMARY OF FINDINGS

Methods for Supporting Basic Science

No single method was clearly preferred for supporting basic science. Strongest support was given to systematically applying a variety of mechanisms to assure that the full capabilities of the dental research community are utilized in conducting basic research in dentistry.

Generally, respondents indicated that basic science should be investigator-initiated as this approach has been most productive in the yield of quality scientific research. The investigator initiatives can come through R01 individual investigator grants, center/large grants, or P01 program project grants broadened to stimulate creativity.

When a clear preference was stated for a single method, it was most frequently for the R01 investigator-initiated grant. Proponents of the R01 grant saw it as the model for open competition of new ideas in basic science.

Regardless of the mechanisms for supporting basic science, there was general agreement that peer review of all research grants, large and small, is critical to assuring scientific quality. Emphasis on peer review reflected the belief that the dental research community can most appropriately set the course for basic science in dentistry and assess the progress being made.

Investigator-Initiated Versus NIDR-Targeted Research

This issue involves whether the direction of dental research should emphasize more thematic, categorical, and noncategorical NIDR-initiated research or individual investigator-initiated research.

The dental research community favored investigator-initiated research for setting the direction of dental science inquiry; many saw the need for targeted research as well. Targeted research was seen as providing the NIDR with the flexibility to address specific areas where a critical need exists.

However, even among those who proposed targeted research for specific areas of importance, the investigator-initiated mechanism was seen as the more appropriate for most research areas. Of those recommending both approaches, nearly all indicated that the majority of the research budget should be allocated for investigator-initiated research.

Those favoring investigator-initiated research believed that it allows investigators to exercise their creativity without the financial and philosophical restrictions of targeted research; produces better science than targeted research; successfully identifies important areas of research; and has the greatest potential for continuing to advance dental science.

Support was given for the P01 program project grant mechanism as a flexible approach combining the best features of the DRIC's and thematic centers. The P30 core grant mechanism, not currently used by the NIDR, was recommended as an approach to strengthen dental research and to help ensure flexibility in the development of centers.

Several principles were suggested for deciding the course of dental research:

- Basic research should predominate.
- Quality of science is preeminently important.
- Peer review is the key to ensuring quality.

- The long-range objective is maximum performance for the dollars invested.
- Rather than predetermine a balance between program-targeted research and investigator-initiated research, flexibility should be maintained.
- The NIDR long-range research plan, "Challenges for the Eighties," provides guidelines for areas needing research.

Continuance of Center Mechanism

There was strong support for continuing the center/large grants in the dental research community. The DRIC's were praised for the valuable contributions they have made to furthering dental research. Numerous advantages of the centers were offered:

- Effective and efficient mechanisms for conducting dental research.
- Provide fruitful sources of investigator-initiated research.
- Facilitate an assembly of a critical mass of researchers from multiple disciplines to address important research problems.
- Permit the interchange of ideas and findings across disciplines.
- Produce high levels of quality research.
- Research benefits from broad university base.
- Center-sized grants help dental schools compete with medical schools.
- Particularly effective for large-scale costly studies required to assess the efficacy of therapeutic or preventive procedures.
- Provide an effective flexible mechanism for funding when funds are limited.
- Beneficial effect on dental education in their parent universities.

A minority recommended that the center/large grants not be continued for the following reasons:

- With current budget limitations, no one center can have competent researchers in all areas.
- Have not been effective overall.
- Served an important purpose to help advance basic dental research but have outlived their usefulness. Thematic and categorical centers are more effective to serve areas needing attention.

- Do not integrate well into the academic program due to their size and cannot be absorbed when unfunded.

The following suggestions were made for modifications in the implementation of the center/large grants:

- Make them fully competitive (details on access to competition given later).
- Subject these grants to a standardized peer review.
- Funding for the centers should be seen as a one-time support mechanism not a lifetime endowment. Possibly use core grant mechanism or a starter grant.
- Fund more, but smaller, centers.
- Nothing magical about five DRIC's. Could fund fewer centers to be decided by competition. If fewer are funded, extra funds could be used for thematic and categorical centers.
- Take this opportunity to reevaluate and refocus goals.

Competition for Center Awards

The dental research community overwhelmingly favored open competition for the center awards. Competition facilitates the optimal use of available funds. There was a belief that more schools and institutions are ready to compete for the centers and that, although not all could qualify, access to the grant competition should be as open as possible. Two moderate positions were expressed. One was that there be initial competition for the centers with subsequent review to provide stability for the centers and to avoid losing the experience the centers gain over a period of time. The second view involved initial competition and subsequent closed competition between those already funded. This position was supported by the rationale that no schools could compete with the currently funded centers; therefore, any competition involving the schools not currently funded would be de facto competition.

The dental research community recognized the implication of open competition on the stability of the centers and the security of research positions. Adequate phaseout periods were recommended as the solution.

Access to Competition for Center Awards

If competition for awards is to be opened up, greater access to center/large grants needs to be ensured. The dental research community suggested several approaches for the NIDR to improve access:

- Improve communication and announcement of the competition. Provide up to 2 years notice, and indicate deadlines, support systems available, and the opportunity for collaborative efforts.

- Provide the widest possible announcement of the competition.

- Two opposing recommendations were made for timing competition. One suggestion was to stagger competition so that one center award would be made each year. The second suggestion was to adjust termination dates of similar centers to coincide so that all awards would be competed at one time. The rationale was that multiple awards would provide more opportunities and a basis of comparison of relative quality.

- Facilitate contacts between the NIDR and potential applicants prior to competition to assist in determining levels of interest and capabilities among potential applicants.

- Set aside funding to be competed for only by developing institutions.

- Promote subcontracting by centers to smaller institutions to provide services.

- Broaden the definition of an acceptable program to allow more institutions to be eligible to compete.

- Fund similar centers for 5 years, rotate, and fund different centers for 5 years. This approach would provide more opportunities by excluding previous award holders from competition for new awards.

Approach to Reviewing Centers

Problems with the review and site visit process for centers were noted during the broad consultation phase. Generally, the major problem was a perceived lack of understanding of the special nature of the centers. Reviewers tend to focus on individual projects within the center. Thus the result is an assessment of the center as a collection of R01-type small grants. The underlying mechanism of the interchange between researchers, interaction with the academic institution, and long-range research planning do not receive appropriate attention. The following suggestions were made for improvements:

- Utilize special review teams selected for expertise in areas of science included in large grant applications to improve the level of understanding of the special nature of large grants.

- Expand the list of qualified reviewers.

- Provide an orientation session for reviewers to provide a common basis for evaluation.

- Achieve a balance in the scientific representation on the review teams to provide a multidisciplinary review process to match the multidisciplinary nature of the centers.

Budget Recommendations

The dental research community generally saw the need for continued and growing support for dental research. Researchers cited the contributions already made by dental research as well as the significant problems that still need to be addressed. Favoring a diversified approach of investigator-initiated and directed research, the dental research community emphasized the need for increasing support for dental research. Increased funding is needed to assure continued strong support for individual investigators as well as teams of researchers.

Mr. NATCHER. And if you would, when you get the transcript back, just go into a little more detail as to these particular centers.

[THE INFORMATION FOLLOWS:]

CENTERS

Following the October 1985 transmission of report to Congress, the NIDR issued a program announcement to inform the dental research community of our planned future use of centers and other large grants. A specific request for applications (RFA) was issued in December 1985 for Research Centers in Oral Biology (RCOB). This RFA reaffirms the Institute's commitment to support multidisciplinary research centers that focus on basic science and related applied problems relevant to oral health and disease. The RCOB program, which provides for open competition, will replace the current Dental Research Institutes and Centers (DRIC) program which has been supported by the NIDR.

Mr. NATCHER. Doctor, are your 1986 and 1987 budgets consistent with the recommendations of the report, would you say?

Dr. LÖE. I think for 1987 we should be able to fund some new centers for research that are mentioned in the report. We may have to postpone the core center grant program and we may not be able to fund other centers at as high a level as we have in the past, but we will go forward with the review of the applications for the Research Centers in Oral Biology when the deadline is over, which is December 1, and from then on we will try to provide the financial framework for realizing that report.

DENTAL SEALANTS

Mr. NATCHER. If you will, Doctor, bring us up to date on the effectiveness of dental sealants. Effective, Doctor?

Dr. LÖE. Yes. The sealants have a history of some 15, 20 years as a research issue. However, in the course of the last ten years we have seen a steady development of better materials and better methodology. By now I think that everybody agrees that the sealants represent a very meaningful complement to fluoride treatment.

As a matter of fact, it has been said that with effective fluoride application to the smooth surfaces of the teeth and sealants for the rough surfaces, we should pretty much be able to eliminate decay on teeth in children.

REDUCED DEMAND FOR SERVICES

Mr. NATCHER. Dr. Löe, improvements in dental health seem to be reducing the demand for dentists. We understand that some dentists are having a hard time making ends meet, making a living.

How serious is this problem, in your judgment, Dr. Löe? Do we have too many dentists?

Dr. LÖE. First of all, there is no question that dental research and the changes in oral disease patterns we have seen over the last ten or 15 years are having an impact on the amount of disease and therefore affect the busyness of a dental practice.

There have been times before when dental practitioners have had problems in filling the day, but these have usually reflected on economic conditions. It seems as if one of the first things to be postponed in hard times is seeing the dentist.

However, this time around, there is no doubt that some of the reductions in the busyness in the dental practices relate to the fact that there is much less disease than we used to have.

We have also seen other market mechanisms at work. For example, the enrollment in dental schools has gone down somewhat dramatically over the past six or seven years. I have been told by the American Dental Association that the reduction in enrollment in dental schools would be equivalent to the closing of 14 dental schools.

Many dental schools have reduced their intake. I think that this was probably warranted, both because of the reduction in the applicant pool, but also because there are probably too many students in many dental schools. These enrollments came about at times when we had capitation programs and incentives to increase enrollments. I think that we will see fewer dentists in the future and there will be an adjustment in the number of dentists in various specialty areas relevant to the changes in disease patterns.

We must not forget, however, that dentists reach only about 60 percent of the population. If the other 40 percent, the remainder of the population were to see the dentist, there would be no overproduction and dentists would have no problem filling the day.

So there are several forces that work in opposing ways to affect dental practice. We will probably see an increased number of people going to the dentist in the future. At the same time, these patients will probably have less disease.

Mr. NATCHER. Mr. Hoyer?

Mr. HOYER. I have no further questions, Mr. Chairman.

Mr. NATCHER. Dr. Löe, we want to thank you and your associates for appearing before our Committee at this time in behalf of your budget request for the fiscal year 1987.

This has been a good hearing, Doctor, and we appreciate it.

Thank you.

The Committee will now recess until 2 o'clock.

[The following questions were submitted to be answered for the record:]

ELDERLY

Mr. Conte. Your Institute has launched a new initiative on oral health in the elderly. What is the aim of this initiative, and what kinds of positive interventions can be made in oral health for our senior citizens?

Dr. Löe. There are several aims to our new initiative. First and foremost, the NIDR has been concerned about the oral health of growing numbers of older persons and wants to expand oral health promotion and disease prevention activities to these groups. The National Institute on Aging and the Veterans Administration share these concerns while representing unique resources and personnel. Together we have developed a Research Agenda on Oral Health in the Elderly, a catalog of Resources, and are in the process of formulating an Implementation Plan. The plan will select research projects in the Agenda that lend themselves to broad collaboration.

There is already information available for the profession and the public that can have beneficial effects on the oral health of the elderly--ways to prevent oral disease; ways to prevent undesirable side effects in the mouth that result from common medications or from radiation therapy or chemotherapy.

We believe that prevention is not just for children and we want to get that message across--as well as encourage research on all aspects of oral changes occurring in aging.

NEUROFIBROMATOSIS

Mr. Conte. Doctor, another disease that I discussed with you last year was neurofibromatosis, and we talked some about the kinds of facial surgery that can now be done. What encouraging news can you give me this year, Doctor, and do you think we have a coherent plan out there to deal with this disease effectively?

Dr. Löe. The NIDR supports basic research on wound healing, bone induction, and nerve and muscle regeneration. The NIDR is also supporting clinical research involving development of new techniques for repair of oro-facial clefts. These studies have led to significant advances in our understanding of tissue repair processes and the factors that control rates of healing. This knowledge should enhance the capabilities of the surgeon faced with the type of extensive craniofacial reconstruction that may be required following removal of the tumors associated with neurofibromatosis which are localized to the craniofacial region.

Neurofibromatosis is a neurogenetic disorder of unknown origin. The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) supports research in this area and recently has announced its interest in establishing one or more multidisciplinary centers for the purpose of investigating epidemiologic, genetic, biochemical and clinical aspects of this and other neurogenetic disorders of infancy and childhood.

INDIRECT COSTS

Mr. Conte. Doctor, I'm going to be going into this in a lot more detail with Dr. Wyngaarden and my friends down at OMB, but I just want to touch on it here. If the present system for awarding indirect costs is left in place for FY 1987, how many grants would you have to eliminate from your estimate to the Subcommittee? Can you give us an estimate on that?

Dr. Löe. Assuming the FY 1987 request level for research project grants and full indirect costs, NIDR would be able to fund 98 grants which would be 12 fewer research project grants for FY 1987.

DENTAL DISEASES

Mr. Conte. Doctor, what kinds of dental diseases seem to run in the family? And what ways have you developed to prevent the transmission of these diseases from generation to generation?

Dr. Löe. The expression "run in the family" can mean that a disease is hereditary and is passed on in the genes. There are a few hereditary diseases that lead to malformations of the teeth and bones such as dentinogenesis imperfecta and osteogenesis imperfecta. We have been studying these diseases in animal models and in patients to determine the nature of the genetic defect but as yet we have no means of prevention. Other examples of dental diseases where there may be increased susceptibilities in families include certain forms of periodontal disease such as localized juvenile periodontitis and prepubertal periodontitis. There is some evidence that individuals affected by these diseases have certain immune cell defects which may be hereditary. Investigators are conducting family studies to clarify the genetic basis for these diseases and develop tests that might identify individuals at risk. Appropriate interventions could then be initiated to prevent these diseases from developing in other family members.

Many common oral and dental diseases are caused by bacteria or other microorganisms and can be transmitted within families in the way other infectious diseases are spread, such as by contact. It is widely thought that the bacteria associated with dental caries, Streptococcus mutans, are transmitted from parents to offspring in routine handling of infants after birth. Similarly, the virus that causes cold sores on the lips could be spread in families by contact. There have been studies exploring the possibility of lowering the risk of transmitting cariogenic bacteria to a child by methods aimed at eliminating the bacteria from the mother. The development of a caries vaccine and the use of genetic engineering methods to alter cariogenic bacteria to non-disease-causing forms are also ways that could prevent transmission of dental caries within families.

Factors of lifestyle, poor dietary choices and oral hygiene habits practiced within families may also heighten the risk of disease running in families, and may also contribute to birth defects such as cleft lip or cleft palate. In addition, there are some systemic diseases with a genetic component that increase the risk for oral and dental diseases. Juvenile diabetes is such a disease and investigators are determining what factors can help identify which children in a family with this disease may be at risk and what sorts of interventions can reduce the risk or ameliorate symptoms and complications of the disease.

ADULT ORAL HEALTH STATUS SURVEY

Mr. Conte. Your justifications also talk about the 1986 Adult Oral Health Status Survey. What kind of information will this survey

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yield, and is the oral health of this country's adult population getting better or worse?

Dr. Löe. The 1986 survey of the Oral Health of U.S. Adults is the most comprehensive study of the oral health status of the adult and aged segments of the population yet undertaken. The results will permit precise estimates of the level of dental caries including recurrent caries in previously restored teeth, caries of root surfaces and the prevalence and severity of periodontal diseases, and will serve as a baseline assessing future trends in disease. Furthermore, we expect that the data will identify population groups and regions of the country in greatest need of preventive and restorative services. Those data are now being analyzed and preliminary results will be available by Fall, 1986.

DENTAL SEALANTS

Mr. Conte. Doctor, the year before last we began talking about the development of dental sealants. How rapidly have dental sealants moved into the field?

--Are we getting good results?

Dr. Löe. Since the NIH Consensus Development Conference on Dental Sealants in December of 1983, the use of sealants among practitioners has grown dramaticaly. Anecdotal evidence includes the following; sealant manufacturers report that sales of sealant have increased sharply; more dental insurance companies are now reimbursing for sealants; and as of last October, 14 state Medicaid Programs now pay for dental sealants. At the time of the Consensus Development Conference, only one state Medicaid Program reimbursed for sealants.

ANTI-CARIES VACCINE

Mr. Conte. Where are we with the testing of a vaccine against tooth decay? Is that now out in the field?

Dr. Löe. We are continuing to seek out the most effective immunogen(s) and are testing them for cross-reactivity with human tissue. Ideally, the immunogen of choice should be produced by methods that will ensure the purity of the product--such as those of biotechnology. At a meeting to review caries vaccine research in January 1986, a distinguished group of investigators recommended proceeding cautiously, building up a body of data from animal studies looking at vaccine dosages, antibody classes, duration of response, levels of cariogenic bacteria in the mouth, and so on. Because the prevalence of caries has been declining and the disease is not life-threatening, the NIDR agrees with the conclusions of the experts that there is no urgency to move on to clinical trials. In the meantime, much can be learned about oral ecology and the immune responses unique to the oral cavity. These conclusions were discussed and endorsed by the National Advisory Dental Research Council.

EXPENDITURES ON DENTAL CARE

Mr. Conte. Doctor, do you have any figures on how much is spent each year in this country on dental care? Is that figure rising or falling as a per capita cost?

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NEW AND COMPETING RESEARCH GRANTS

Mr. Early. With the original amount available for FY 86 and under the revised FY 86 proposal, NIDR would be able to fund 149 new and competing research grants. Under the Administration's FY 87 proposal, NIDR will fund only 110, or 39 fewer. What areas of research would be affected by this reduction?

Dr. Löe. Probably all areas of research will be affected by the proposed reduction of new and competing grants. As in the past, funding of projects will be based on peer review. The NIDR, however, may end up having to reduce new support for certain areas of research in order to maintain progress in other essential areas. The extent to which this is likely to happen will depend on the scope of the research being proposed and the efforts currently being supported.

APPROVED GRANTS

Mr. Early. What percentage of approved grants would be funded under the FY 86 revised and FY 87 budget requests? How does this compare to your original FY 86 estimates? How does it compare to FY 85?

Dr. Löe. Under the FY 86 revised budget NIDR will fund 42.8% of its approved grants. In the FY 87 budget 31.3% of approved grants will be funded. In FY 85, 41.2% of approved grants were funded.

DOWNWARD NEGOTIATIONS

Mr. Early. The budget justification states that there will be downward negotiations of 13.6% and 6.4% in competing and non-competing grants, respectively. Will each grant be reduced by these amounts, or are these averages?

Dr. Löe. The downward negotiations of 13.6% and 6.4% in competing and non-competing grants respectively represent average reductions required to fund the number of research grants allocated to the Institute. The reduction will be negotiated individually with each grantee in order to minimize adverse effects on research progress.

Mr. Early. Historically, non-competing research grants have been funded at close to the full commitment levels (99%). Why should these grants be funded at less than the approved levels after having been reviewed?

Dr. Löe. The reduction in the overall budget has necessitated reductions in all funding mechanisms in order to maintain a reasonable level of support for new and competing grants.

RESEARCH CENTERS

Mr. Early. Although the same number of research centers (16) will be supported under the post-sequestration level as under the FY 86 enacted level, there will be a reduction of $598,000. How will this reduction impact the centers program?

--Will each center share evenly in this reduction?

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Dr. Löe. According to the Department of Commerce, the national expenditures for personal dental services were $19.8 billion in 1984. The 1985 figure is not final, but it is estimated to be $21.0 billion.

Growth in expenditures has slowed dramatically since 1970 for a number of reasons, including community water fluoridation, better oral hygiene habits, and preventive services provided by practicing dental personnel. In constant 1982 dollars per capita expenditures for personal dental services have actually declined from $75.55 in 1982 to $72.30 in 1985.

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Dr. Löe. The NIDR has recently issued a request for applications (RFA) for research centers in oral biology (RCOB) and anticipates making several awards under this new program in FY 87. Since the RCOB program replaces the current Dental Research Institutes and Centers program (DRIC), there will be no increase in the overall number of centers. The reduction in funds for the centers program will be achieved by decreasing the size of the new RCOB centers and by downward negotiation of existing center awards. All the centers, competing as well as non-competing, will share in the reduction.

Mr. Early. According to the justification 16 centers will be supported in FY 87, the same as in FY 86, but at a level of $11,790 million as compared to $13,307 million under the FY 86 revised level. This will require downward negotiations of 11.4%.

--Will all centers be reduced by the same amount?

Dr. Löe. The reduction in funds for the centers program will be achieved by decreasing the size of the new RCOB centers and by downward negotiation of existing center awards. All the centers will share in the reduction.

Mr. Early. Will these reductions apply to both competing and non-competing centers? How were these amounts arrived at?

Dr. Löe. Yes. Reductions apply to both competing and non-competing centers.

Mr. Early. Were these figures arrived at after careful and thoughtful review--or did you have a set figure you had to work towards?

Dr. Löe. Thoughtful review was made of all funding mechanisms to adjust to the level of the FY 1987 budget. The reduction in funding for research centers is comparable to the reductions in the other activities in the FY 87 budget.

Mr. Early. Doctor, will you summarize with some specificity, the effect the proposed reduction in size and scope of the centers program will have on NIDR's program plans--both immediate and long-range.

--What effects will these cuts have on the programs at the centers?

Dr. Löe. The immediate impact of the budget reduction and the limitation on numbers of centers is to prevent NIDR from realizing its plans for a core grant program and additional categorical/thematic centers. The long-range effect of the proposed reduction on size and scope of the centers program will diminish the research effort. Many projects may have to be postponed or scaled back.

NEW RESEARCH CENTERS

Mr. Early. The justification notes that a request for applications for new Research Centers in Oral Biology has been issued. Because the FY 87 request does not allow for any additional centers (total number remaining 16), how will these centers be accommodated?

Dr. Löe. The RCOB program replaces the current DRIC program. Two of the five DRIC centers reach the end of their award period in FY 87 freeing up two center awards. NIDR anticipates that all five DRICs will participate in the open competition for the new RCOB awards. Thus the final number of RCOB awards could go as high as five without increasing the NIDR's overall number of centers.

DIRECT COSTS

Mr. Early. Doctor, in the past, when you've had reductions in direct costs, what has been the effect? Are research teams disbanded? Are projects that are postponed or temporarily scaled back resumed?

Dr. Löe. Many projects are scaled down or postponed and training and career development opportunities will be lost. To the extent that the research teams have been kept intact, they will be in a position to resume an all-out effort once full funding is resumed.

NEW INITIATIVES

Mr. Early. Will the FY 87 budget request enable NIDR to undertake any new initiatives?

Dr. Löe. The Institute had planned to support selected projects in the recently completed Research Agenda on Oral Health in the Elderly developed in collaboration with the National Institute on Aging and the Veterans Administration. The NIDR will still distribute the agenda to interested parties and make known the interests of the three agencies in this important area in order to stimulate activity and encourage applications for research grants.

ADDITIONAL FUNDS

Mr. Early. If an increase over the FY 87 request is provided, how would you use these additional funds?

Dr. Löe. The NIDR will use the additional funds to increase funding for grants, centers, contracts and all other mechanisms used by the NIDR, including the various research training and career development award programs.

LACK OF FUNDS

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed by lack of funds in the FY 87 budget?

—Please provide, for the record, a list of these along with a brief description and the funding requirements associated with each.

Dr. Löe. The expected growth in research in premier areas of dental research, e.g., recombinant DNA studies, immune mechanisms, vaccine research, studies of new means of preventing and treating oral diseases, will be slowed by an anticipated reduction in the number of new research projects that can be funded in FY 1987, amounting to some $2.5 million in support. In addition the NIDR had hoped to be able to fund a minimum of 5 new Research Centers in Oral Biology which would require $3.0 million in addition to the total now allotted to this program. Further, the FY 1987 budget will not allow the initiation of the new Core Center program (P30s). The NIDR had anticipated funding five such centers for a total cost of $1.5 million.

Another important new initiative which will be affected by budget reductions is support of research proposed in the recently completed Research Agenda on Oral Health in the Elderly developed in collaboration with the National Institute on Aging and the Veterans Administration. The NIDR had estimated a minimum of $500,000 for this new initiative.

RESEARCH INITIATIVES DELAYED

Mr. Early. Doctor, will any significant research initiatives currently underway be halted or seriously delayed due to FY 87 funding levels?

--To what extent will there be major reductions in the scope of ongoing or new initiatives because of the FY 87 funding levels?

--For the record, please provide a list of these along with a brief description and the amounts associated with each initiative.

Dr. Löe. Among significant areas of dental research that will be affected by FY 1987 budget reductions are genetic and molecular biology studies of craniofacial morphogenesis and teratogens, bone remodeling and repair, wound healing, and both immune and non-immune defense mechanisms in response to infection. Basic research on the neural substrates of pain transmission and modulation aimed at developing new analgesic agents will be delayed. Other activities affected include categorical research on dental caries and the periodontal diseases, on oral herpes, oral cancers and other oral soft tissue diseases, and on bone and joint diseases such as osteoarthritis and osteoporosis.

Behavioral and social science research to facilitate transfer of research findings to the public and to the profession will decline. This includes research on ways to combat dental fear and anxiety and encourage compliance in appropriate oral hygiene methods and utilization of dental services. Research conducted within the Institute's Epidemiology and Oral Disease Prevention program will be reduced. This will result in a limited number of clinical trials as well as population studies to identify risk factors for oral diseases and disorders. This slowing of progress of research is reflected in an estimated $6.2 million reduction in the level of support available for ongoing research project grants, center grants, and contracts.

Research training and career development programs will have to be cut back. Directly affected will be the Dentist Scientist Award program. The next class of candidates will not be able to be admitted at those institutions that have active Dentist Scientist grants at a time when the Institute of Medicine of the National Academy of Sciences has called for a substantial increase in the preparation of dentist investigators. Other career development awards (K04s) and support of postdoctoral and other fellowships (F-awards) as well as research training (T-awards) will be diminished. In turn, the T-35 award (short-term training) which is a highly successful program for introducing dental students to careers in research, will have to be curtailed. To support the planned addition of the next class in career development and research training programs would require an additional $2.1 million.

RESEARCH AND DEVELOPMENT CONTRACTS

Mr. Early. Under the revised FY 86 level, due to sequestration, only 33 research and development contracts will be supported, as compared to 35 under the FY 86 enacted level. Associated with this reduction is $202,000. How will this reduction be taken, and what impact will it have on your current and future research initiatives?

Dr. Loe. Two research and development contracts will be postponed.

Mr. Early. Doctor, could you give us a few examples of how the Institute utilizes this research and development contract mechanism?

Dr. Loe. The Institute uses the contract mechanism for a broad range of activities. The following ongoing contracts provide examples of this range:

--Epidemiological Study of Oral Health in Adults.

--Clinical Studies of Periodontal Diseases in Older Adults.

--Interaction of Oral Structures on Restorative Materials.

--Improved Manufacturing Methods for the Intraoral Fluoride-releasing Device.

--Relationship of Dietary intake to Caries Incidence.

--Development of Antigens and Adjuvants for Induction of Caries Immunity.

--Cost Effectiveness of a Combined Sealant Self-Applied Fluoride Program.

Mr. Early. The FY 87 request will support 34 research and development contracts as compared to the FY 86 revised level of 33, and the FY 86 enacted level of 35.

--Does this "unstableness" have any adverse impact on your overall programs? If yes, please explain.

--What impact will it have on NIDR's current research activities?

Dr. Loe. A reduction of this small magnitude in the amount of contract funds has little impact. The Institute sets priorities and can postpone lower priority studies or clinical trials.

CLINICAL TRIALS

Mr. Early. How many clinical trials will be supported under the FY 86 revised level?

--For the record provide a list of these and indicate the total amount of funding associated with each, broken out for each year.

Dr. Loe. NIDR will support 12 clinical trials under the FY 86 revised level, they are as follows:

	FY 83	FY 84	FY 85	Revised FY 86
Prevention of Transmission of S. Mutans From Mothers to Children	$170,609	$242,106	$128,199	$128,199
Clinical Trial of Effect of Prenatal Fluoride Supplements in Preventing Dental Caries	112,324	103,691	128,588	128,588
Cost-Effectiveness of a Combined Sealant Self-Applied Fluoride Program	204,548	224,933	134,730	134,730
Clinical Trial of an Adhesive Material	167,122	133,754	133,754	133,754
Clinical Trial of the Efficacy of Sodium Fluoride Mouthrinses in Preventing Dental Caries in Adults	191,520	82,073	15,000	15,000
Clinical Studies of Periodontal Diseases in Older Adults	363,903	250,000	250,000	250,000
Clinical and Laboratory Evaluations of Dental Restorative Materials	133,282	96,085	144,130	194,775
Clinical Evaluation of Restorative Materials	75,966	77,037	83,206	83,206
Clinical Evaluation of Alternative Crown and Bridge Systems	34,200	245,825	245,825	265,125
Clinical Effect of Toothbrushing with 0.4% Stannous Fluoride Gel			213,331	
Clinical Evaluation of Fluoride Slow-Release Intraoral Devices				70,000
Efficacy of Various Pharmacologic Agents in Blocking UV Induced Herpes Simplex				100,000
Total	1,453,474	1,455,504	1,476,763	1,503,377

Mr. Early. How many of these are new clinical trials?

Dr. Löe. Two of the above mentioned are new clinical trials. They are (1) Clinical Evaluation of Slow-Release Intraoral Devices, and (2) Efficacy of Various Pharmacologic Agents in Blocking UV Induced Herpes Simplex.

Mr. Early. Will you be able to start any new clinical trials in FY 87?

--if yes, provide a list and the cost associated with each.

Dr. Löe. No. NIDR will not start any new clinical trials in FY 87.

Mr. Early. Doctor, will you have to curtail any ongoing clinical trials with your FY 87 budget request? If so, which ones?

Dr. Löe. The Institute's clinical trials will not be curtailed.

Mr. Early. Are there any high priority clinical trials which are ready but cannot be initiated because of lack of funds in the FY 87 request. If so please provide a list of these, along with a brief description and the associated costs, including first year cost.

Dr. Löe. We have two clinical trials that will be postponed. They are the following:

--Clinical Evaluation of the Relative Efficacy and Safety of Intravenous Premedication in Dental Outpatients.

The clinical trial consists of a multicenter, parallel groups, double-blind comparison of prototype drug regimens administered intravenously to alleviate patient apprehension and pain during outpatient dental procedures. The results will provide the first scientifically derived data on the relative safety and efficacy for this widely used yet controversial therapeutic modality. First year cost is $225,000; total cost is estimated at $425,000.

--Diabetes Control and Complications Trial (DCCT), Oral Complications.

This overall project is a large multicentered long term clinical trial (at least 5 years) to determine whether tight control of blood glucose prevents and/or delays secondary complications (including periodontal disease) in juvenile type, or insulin dependent diabetes mellitus (IDDM). The project is being coordinated by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases and participants include The National Eye Institute and the National Heart, Lung, and Blood Institute. NIDR would support oral periodontal examinations and perhaps X-rays and limited microbiology studies. First year cost is $150,000; total cost is estimated at $300,000.

OTHER RESEARCH RELATED

Mr. Early. Doctor, under the "other research related" category I see the number of projects supported will drop to 65, as compared to 72 under the FY 86 revised level and 75 under the FY 86 enacted level. First of all, what types of activities do you support under this heading? And secondly, how will this reduction be achieved?

Dr. Löe. The "other research related" category provides support for small grants, conference grants and minority biomedical research grants. Most of the funds in this category are used to support small grants, a highly successful program which provides one-year funding for pilot projects and other short-term research efforts. These awards are limited to $15,000 each; therefore cuts will be to the number of awards rather than to the amount of the award itself. The NIDR will also reduce conference support, but will maintain support for meritorious minority biomedical research grants.

AIDS RESEARCH

Mr. Early. Doctor, in laymen's terms, would you briefly tell us what new findings NIDR has uncovered with regards to AIDS?

Dr. Löe. NIDR scientists have been studying the immunological defects of particular white blood cells--monocytes--in AIDS patients. These cells are among the body's first line of defense against infection and their inability to function effectively contributes to the painful and severe oral infections that occur quite commonly in AIDS patients. These include candidiasis (caused by the fungus Candida albicans) and oral herpes lesions.

The NIDR scientists have established that monocytes in AIDS patients exhibit decreased migration towards infectious sites. Not only do the cells fail to accumulate at the site of infection, but they also cannot efficiently kill certain infectious agents, enabling the persistence and dissemination of Candida and other life-threatening infections. The investigators are currently exploring the mechanisms underlying the abnormal monocyte functions and have shown that this cell can be directly infected with HTLV III/LAV, the virus responsible for AIDS. Their current studies are focusing on the mechanisms whereby the virus infects the monocytes with the intention of finding chemotherapeutic and immunomodulatory agents to prevent or reduce infection and depressed function of this cell.

NIDR scientists have also been studying abnormalities in other immune cells, and have been collaborating with other NIH scientists in clinical studies of AIDS patients, noting particular bacterial infections of the gastro-intestinal system. NIDR is expanding research on AIDS to include studies of changes in oral tissues and fluids that occur in the course of development of AIDS or at later stages of the disease. Additional collaborative studies of AIDS patients are planned which include trials of new therapies to treat the disease.

PERIODONTAL DISEASE

Mr. Hoyer. We are aware of the efforts you are conducting and supporting to prevent periodontal disease. Please provide a status report on new chemotherapeutic approaches to the control of plaque and gingivitis. When will the American public begin to benefit from this preventive approach?

Dr. Löe. Several chemotherapeutic approaches are being tested for their therapeutic value in plaque control. One agent that has been used widely in Europe as a mouth rinse, chlorhexidine, is effective in controlling the development of supragingival plaque and gingivitis. Approval by Federal regulatory agencies is currently being sought for use of the agent in this country. Also, the NIDR has begun a clinical trial of a stannous fluoride mouth rinse to control plaque and gingivitis. A preparation of this type may be marketable within two or three years. In addition, the NIDR is supporting research at nonprofit institutions and at small business enterprises to develop controlled release antibacterial agents which will not only control supragingival plaque associated with gingivitis, but will also prevent bacterial growth deep in periodontal pockets for long periods, perhaps for weeks and months. Such agents with appropriate controlled release delivery systems, may be available within three to four years.

SMALL BUSINESS PROGRAM

Mr. Hoyer. The Small Business program offers the NIH the opportunity to use the talents and the ideas of small commercial firms to do research and to help transfer the benefits of research to the American public. What use has the NIDR been able to make of this program? Do any of the NIDR's Small Business projects have the potential to be commercially successful?

Dr. Löe. NIDR has been able to initiate a number of interesting Small Business Innovation Research (SBIR) projects, including an attempt to develop new tools and materials to be used in clinical research and practice, as well as studies to devise antiherpes agents. One of the most promising endeavors involves the development of a highly innovative new probe to assess periodontal disease by measuring pocket depth and attachment loss. Now in the Phase II stage of development, this project has excellent potential for commercial success. Another promising project is aimed at treating periodontal diseases by means of the controlled release of chemotherapeutic agents, such as the antibiotic tetracycline. This project has so far been funded as a Phase I project, but a Phase II application has been received and will soon be reviewed.

One of the NIDR's SBIR projects in particular provides an excellent example of how basic dental research can lead to technological innovation. A new company has been formed which is on the verge of marketing a superglue with widespread applications in dentistry, medicine, and shipping. This company is an outgrowth of 10 years of basic research funded by the NIDR at the University of Connecticut Health Center to learn more about the extraordinary glue that marine animals--common mussels--produce that enables them to adhere to structures underwater. Most adhesives need dry surfaces to be effective. The mussel's glue works in a wet, saline environment as well as a dry one.

The main ingredient in the mussel glue has now been identified and plans call for reproducing the adhesive in quantity. Dentists, foresee using the glue as a sealant, as a material for filling cavities, and as an adhesive for bonding teeth. Surgeons are interested because the glue could be used in operations to coat sutured tissue to prevent infection. The adhesive could also hold together small broken bones or tendons. The Navy hopes to use a form of the substance to coat the hulls of ships to prevent fouling by marine growth and corrosion. In August, 1985 the NIDR awarded the company a Small Business Innovative Research Grant. Recently, government approval for a patent on the composition of the basic structure of the protein isolated from the mussel glue was granted to the University of Connecticut, giving the company exclusive rights to this adhesive. Within about two years, it is expected that the adhesive will be available for topical use in dentistry. The company is also making plans to produce the adhesive in large quantities for industrial use through genetic engineering techniques.

BIOTECHNOLOGY

Mr. Hoyer. You have emphasized how far dental research has come in joining mainstream biomedical research, especially in areas of biotechnology. Would you provide specific examples of progress in this area?

Dr. Löe. Here are several examples:

Recombinant DNA methodology is being used to study potential periodontal pathogens such as Actinomyces viscosus and their establishment in the oral cavity. The genes coding for the fine filaments that allow the organisms to attach to tissue or other bacteria have been cloned and the filaments are being studied to find ways to prevent attachment and resulting disease.

A recombinant herpes simplex virus (HSV) vaccine combines vaccinia virus with the gene for glycoprotein D of HSV-1. The vaccine proved effective in tests in the mouse against lethal and primary HSV-1 and HSV-2 (genital HSV) infections.

Recently genes for the B chain of laminin have been cloned. Laminin is a structural glycoprotein unique to basement membrane, a layer of tissue which underlies epithelial and mucosal tissues. Laminin has an effect on growth and development of a variety of cells. It also is a focus of interest in cancer research since metastatic cells have a strong affinity for laminin and a specific enzyme that can dissolve the membrane and invade tissues.

NIDR scientists have cloned the genes for osteonectin and bone proteoglycan, two constituents of bone matrix important in bone formation. Alterations in large molecules--proteoglycans--formed in joint tissue are being studied as a clue to osteoarthritis pathology. Monoclonal antibodies have been made against osteonectin. A radioimmune assay has been developed and is being used to measure serum levels of osteonectin to aid in diagnosis of bone diseases and as an indicator of efficacy of treatment. A new time-saving method for isolation of cells producing monoclonal antibodies has been developed. This method is being used to study antibodies made against normal body constituents as occurs in autoimmune diseases.

CENTERS AND LARGE GRANT PROGRAM

Mr. Hoyer. This past year, the NIDR submitted a report to Congress on its Centers and Large Grant program. Please give us an update on the progress you have made in implementing the plan. How will the proposed FY 87 Budget affect these plans?

Dr. Lōe. A program announcement has been issued regarding our planned future use of centers and other large grants. We have also issued a request for applications (RFA) for Research Centers in Oral Biology (RCOB). With an application receipt date of December 1, 1986 this RFA reaffirms the Institute's commitment to support multidisciplinary research centers that focus on basic science and related applied problems relevant to oral health and disease. The RCOB program replaces the current Dental Research Institutes and Center (DRIC) program and sets up open competition for these center awards. The RFA indicates that NIDR anticipates making several awards in FY 87 and projects a minimum expenditure of $3,000,000.

With the addition to 3 new categorical/thematic centers, the total number of research centers supported in FY 1986 reached 16. The FY 1987 budget maintains this number but calls for a reduction of $1,517,000 of support, $905,000 of which is from the monies available to support the DRIC/RCOB program. These overall reductions will be obtained by reducing all center awards. Since just 2 center grants terminate in FY 87, it will be possible to support, at a reduced level, only 2 of the new RCOB grants. In keeping with the FY 87 budget, the NIDR will also defer the initiation of the core grant (P30) program and any further expansion of the categorical/thematic center program that were called for in the report.

AIDS-RELATED RESEARCH

Mr. Porter. Given the focus of the NIH on AIDS-related research, what is being done to identify risk factors related to the transmission of AIDS to oral health professionals and the protection of oral health professionals from contracting AIDS?

Dr. Löe. Although no case of transmission of AIDS virus to oral health professionals in the normal course of treating AIDS patients has yet been reported, the HTLV-III virus has been isolated from saliva so the potential for transmission is recognized. Because the oral transmission of other viral diseases, such as hepatitis and herpes, is relatively common, investigations of AIDS virus in the mouth is receiving high priority.

The NIDR is initiating a collaborative research effort with the Walter Reed Army Medical Center to address a variety of questions on oral aspects of HTLV-III infection and AIDS. Part of this study will collect needed information on the frequency of occurrence of AIDS virus in saliva, the source of the virus, and whether the virus occurs in the mouth in early stages of the infection before symptoms are noted.

For the protection of professionals and patients from exposure to infection in the dental office--not only to AIDS but to other transmissible diseases--the NIDR believes that dental professionals should wear masks, gloves, and goggles. The Center for Disease Control (CDC) is now developing guidelines. NIDR plans to obtain base-line information on knowledge, attitudes and current practices concerning the prevention of transmission of infectious diseases in dental offices and clinics. Given this information, the Institute will develop appropriate educational programs for dental practitioners and dental auxiliaries. Concomitantly, we are developing educational materials to help educate patients in the dental office about the need for employment of infectious control procedures.

PREVENTIVE DENTAL CARE

Mr. Porter. Given that the promotion of preventive dental care is inherent to the mission of NIDR, in what kinds of activities is the Institute involved to insure all Americans receive preventive dental care?

Dr. Löe. The NIDR cannot ensure that all Americans receive preventive dental care, however the Institute is responsible for transferring research results about preventing oral diseases to health care providers and the general public. A substantial amount of NIDR research has been devoted to establishing the efficacy of fluorides in preventing decay.

The Institute has promoted community water fluoridation and the use of fluorides in other forms. As a result, the majority of Americans are enjoying the benefits of water fluoridation and over 90% of the public use fluoride-containing dentrifices. Other prevention regimens such as the use of dental sealants have also been advocated by the Institute and are increasingly being used in dental offices to protect the rough surfaces of children's teeth from decay. The percent of the public seeing a dentist each year has been increasing. These are examples of the kinds of prevention-oriented research and science transfer activities the Institute pursues to demonstrate to the profession and to the public that dental diseases can be prevented and that no one need ever lose a tooth to disease.

NIDR science transfer activities include the publishing of research results, sponsoring conferences, and developing educational materials for use by health care providers to increase their knowledge and understanding of preventive regimens. In addition, the NIDR develops collateral educational materials, such as leaflets, posters, brochures and films to educate the public and supports social science and behavioral research to develop interventions that will aid individuals in adopting appropriate oral health promotion and disease prevention behaviors. These include programs to help individuals overcome dental anxiety and fear of pain.

DENTAL HYGIENIST

Mr. Porter. I understand that NIDR is about to conclude its investigation into the adult incidence of periodontal disease. Because people are living longer and retaining more of their teeth with the possibility of a higher incidence of untreated dental disease, how do you foresee integration of new technologies and preventive care strategies with the role of the dental hygienist?

Dr. Löe. Just as dental hygienists have played an active role in the prevention of both dental caries and periodontal diseases in the past, their continued involvement is anticipated in the future. Their specific roles could include carrying out essential preventive services as part of the dental team, aiding technology transfer to the public, dental hygiene students, and allied health professionals, and conducting applied and behavioral research in clinical, academic and institutional settings.

With emerging new preventive technologies it is expected that the duties of the dental hygienist will increase. Since 1977 the Institute mails to all dental hygiene departments copies of relevant educational materials such as conference proceedings, research results and new materials with which to educate patients. The Institute will continue these efforts as new scientific information becomes available.

DEPARTMENT OF HEALTH, AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

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NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

For carrying out section 301 and Title IV of the Public Health Service Act with respect to dental diseases, [$103,377,000] *$96,482,000. (Department of Health and Human Services Appropriation Act, 1986.)*

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Amounts Available for Obligation 1/

	1985	1986	1987
Appropriation	$100,688,000	$103,377,000	$96,482,000
Enacted administrative reduction	---	-95,000	---
Sequester order	---	-4,441,000	---
Proposed rescission	---	---	---
Subtotal, adjusted appropriation	100,688,000	98,841,000	96,482,000
Comparative transfer to: 2/ Office of the Assistant Secretary for Health, for AIDS Projects	-97,000	-655,000	---
Comparative Transfer from: Office of the Director for charges in the Central Services financing mechanisms and formulas	+303,000	---	---
Subtotal, adjusted budget authority	100,894,000	98,186,000	96,482,000
Unobligated balance, start of year	---	+70,000	---
Unobligated balance, end of year	-70,000	---	---
Unobligated balance, lapsing	-204,000	-75,000	---
Total, obligations	100,620,000	98,181,000	96,482,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1985 -- $82,000; 1986 -- $260,000; 1987 -- $3,028,000, of which $2,768,000 is for AIDS projects.

2/ The comparable amount for the appropriation is $684,000.

National Institute of Dental Research

Budget Mechanism
(Dollars in thousands)

	1986 1/ 2/ Appropriation		1986 Available after 1/ 3/ Sequestering		1986 1/ 3/ Revised		1987	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research grants:								
Research projects								
Noncompeting projects...............	248	$28,926	248	$27,682	248	$27,682	269	$30,561
Administrative Supplementals........	—	—	—	—	—	—	—	—
Competing projects:								
Renewal...........................	60	7,872	60	7,309	60	7,309	48	5,568
New...............................	89	10,211	89	10,000	89	10,000	62	7,115
Supplemental......................	—	—	—	—	—	—	—	—
Subtotal, competing............	149	18,083	149	17,309	149	17,309	110	12,683
Subtotal, research............ projects....................	397	47,009	397	44,991	397	44,991	379	43,244
Research centers								
Specialized/Comprehensive Ctrs.......	11	6,306	11	6,035	11	6,035	11	5,423
Dental research institutes...........	5	7,599	5	7,272	5	7,272	5	6,367
Subtotal, research................. centers..........................	16	13,905	16	13,307	16	13,307	16	11,790
Other research								
Research career program..............	58	4,204	55	4,023	55	4,023	58	4,204
Minority biomedical support..........	—	117	—	112	—	112	—	117
Other research related...............	75	1,311	72	1,255	72	1,255	65	1,135
Subtotal, other research...........	133	5,632	127	5,390	127	5,390	123	5,456
Total, Research Grants.................	546	66,546	540	63,688	540	63,688	518	60,490

Training								
Individual awards:								
Noncompeting	29	725	29	721	29	721	35	875
Competing:								
Renewal	—	—	—	—	—	—	—	—
New	21	525	19	475	19	475	7	175
Subtotal, individual	50	1,250	48	1,196	48	1,196	42	1,050
Institutional awards:								
Noncompeting	140	2,890	140	2,863	140	2,863	137	2,877
Competing:								
Renewal	—	—	—	—	—	—	—	—
New	22	422	16	307	16	307	25	435
Subtotal, institutional	162	3,312	156	3,170	156	3,170	162	3,312
Total, training	212	4,562	204	4,366	204	4,366	204	4,362
Research & Development Contracts	35	4,686	33	4,484	33	4,484	34	4,586
					FTEs		FTEs	
Intramural Research		20,004		19,135	255	19,135	255	20,303
Research Management and Support		6,870		6,508	74	6,508	74	6,741
Total, NIDR		102,668		98,181		98,181		96,482

1/ Reflects an enacted administrative reduction of $95,000, and a carryover in unobligated funds of $70,000.

2/ Reflects a comparable transfer of $684,000 to the Office of the Assistant Secretary of Health for AIDS projects.

3/ Reflects a consultant services (Section 515 of the Treasury-Postal Services Appropriation Act, 1985) withholding of $75,000, and a comparable transfer of $655,000 to the Office of the Assistant Secretary of Health for AIDS projects.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

CROSSWALK - 1986 Appropriation

(Dollars in thousands)

Program Activity	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management and Support	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional				
Diseases of the teeth and supporting tissues..	$34,665	$5,401	$4,674	$612	$2,352	$4,686			$52,390
Disorders of structure, function, and behavior..	12,344	905	958	638	960				15,805
Dental research institutes..............		7,599							7,599
Intramural research.......							$20,004		20,004
Research management and support.............								$6,870	6,870
Total..........	47,009	13,905	5,632	1,250	3,312	4,686	20,004	6,870	102,668

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

CROSSWALK - 1986 Available After Sequestering
and
1986 Revised Request

(Dollars in thousands)

Program Activity	MECHANISM								
	Research Grants			Training Programs					
	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management and Support	Total
Diseases of the teeth and supporting tissues..	$32,862	$5,169	$4,473	$ 585	$2,251	$4,484			$49,824
Disorders of structure, function, and behavior..	12,129	866	917	611	919				15,442
Dental research institutes..............		7,272							7,272
Intramural research.......							$19,135		19,135
Research management and support.............								$6,508	6,508
Total..........	44,991	13,307	5,390	1,196	3,170	4,484	19,135	6,508	98,181

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

CROSSWALK - 1987 Congressional Justification

(Dollars in thousands)

	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management and Support	Total
Program Activity	Research Projects	Research Centers	Other Research	Individual	Institutional				
Diseases of the teeth and supporting tissues..	$31,521	$4,663	$4,518	$514	$2,352	$4,586			$48,154
Disorders of structure, function, and behavior..	11,723	760	938	536	960				14,917
Dental research institutes..............		6,367							6,367
Intramural research.......							$20,303		20,303
Research management and support.............								$6,741	6,741
Total..........	43,244	11,790	5,456	1,050	3,312	4,586	20,303	6,741	96,482

NATIONAL INSTITUTE OF DENTAL RESEARCH

Summary of Changes

1986 Current estimated obligations	$ 98,181,000
1987 Estimated obligations	96,482,000
Net change	-1,699,000

	1986 Base	Change from Base
Increases:		
A. Built-in:		
1. Within grade increase	$13,304,000	+80,000
2. Federal Employees compensation fund increases	34,000	+10,000
3. Unemployment compensation increase	24,000	---
4. FTS rate increase	176,000	+68,000
5. Payment for service and supply services	3,372,000	+168,000
6. Increased cost of laboratory supplies, materials and other expenses	5,673,000	+577,000
Subtotal		+903,000
B. Program:		
1. Research projects:		
a. Noncompeting continuations converting from competing status	27,682,000	+18,651,000
b. Competing (new, renewals and supplementals)	17,309,000	+12,753,000
2. Research centers:		
a. Noncompeting continuations converting from competing status	12,402,000	+1,947,000
b. Competing completed or converting to noncompeting status	905,000	+72,000
3. Other research:		
a. Noncompeting continuations converting from competing status	4,135,000	+444,000
b. Competing (new and renewals)	1,255,000	+1,135,000
4. Individual training awards:		
a. Noncompeting continuations converting from competing status	721,000	+475,000
b. Competing (new and renewals)	475,000	+175,000

Summary of Changes -- continued

	1986 Base Amount	Change from Base Amount
5. Institutional training awards:		
a. Noncompeting continuations converting from competing status	2,863,000	+403,000
b. Competing (new and renewals)	307,000	+435,000
6. Research and development contracts:		
a. Continuations	3,657,000	+1,003,000
b. Competing	827,000	+624,000
7. Intramural Research:		
a. Program increase in high priority areas	19,135,000	+498,000
Subtotal		+38,615,000
Total increases		+39,518,000
Decreases:		
A. Program:		
1. Research projects:		
a. Noncompeting completed or converting to competing status	27,682,000	-15,772,000
b. Competing completed or converting to noncompeting status	17,309,000	-17,309,000
2. Research centers:		
a. Noncompeting completed or converting to competing status	12,402,000	-2,631,000
b. Competing completed or converting to noncompeting status	905,000	-905,000
3. Other research:		
a. Noncompeting completed or converting to competing status status	4,135,000	-258,000
b. Competing completed or converting to noncompeting status	1,255,000	-1,255,000
4. Individual training awards:		
a. Noncompeting completed or converting to competing status status	721,000	-321,000
b. Competing completed or converting to noncompeting status	475,000	-475,000
5. Institutional training awards:		
a. Noncompeting completed or converting to competing status	2,863,000	-389,000
b. Competing completed or converting to noncompeting status	307,000	-307,000

Summary of Changes -- continued

	1986 Base	Change from Base
6. Research and development contracts:		
a. Continuation..................	3,657,000	-698,000
b. New..........................	827,000	-897,000
Subtotal, program......		-41,217,000
Total, decreases..........		-41,217,000
Total, net change....................		-1,699,000

National Institute of Dental Research

Budget Authority by Activity
(Dollars in thousands)

	1986 1/ Appropriation	1986 Available after 2/ Sequestering	1986 2/ Revised		1987	
	Amount	Amount	FTEs	Amount	FTEs	Amount
Diseases of the teeth and supporting tissues.....	$52,390	$49,824	—	$49,824	—	$48,154
Disorders of structure, function, and behavior.....	15,805	15,442	—	15,442	—	14,917
Dental research institutes.................	7,599	7,272	—	7,272	—	6,367
Intramural research..........	20,004	19,135	255	19,135	255	20,303
Research management and support...............	6,870	6,508	74	6,508	74	6,741
Total Obligations..............	102,668	98,181	329	98,181	329	96,482
Unobligated balance, start of year..............	-70	-70		-70		---
Unobligated balance, lapsing....................	---	75	--	75	--	---
Total budget authority.......	102,598	98,186	329	98,186	329	96,482

NOTE: All 1986 columns reflect an enacted administrative reduction of $95,000.

1/ Reflects a comparable transfer of $684,000 to the Office of the Assistant Secretary of Health for AIDS projects.

2/ Reflects a comparable transfer of $655,000 to the Office of the Assistant Secretary of Health for AIDS projects.

National Institute of Dental Research

Obligations by Object

	1985 Actual	1986 Estimate	1987 Estimate
Total number of full-time permanent positions.................	285	285	285
Total compensable workyears:			
Full-time equivalent employment.....	328	334	334
Full-time equivalent of overtime and holiday hours........	4	4	4
Average ES salary.....................	$66,232	$66,232	$66,232
Average GS grade......................	9.14	9.14	9.14
Average GS salary.....................	28,224	28,224	28,224
Average salary, grades est. by act of July 1, 1944 (42 USC 207)........	35,361	35,361	35,361
Average salary of ungraded positions..	23,206	23,206	23,206
Personnel compensation:			
Full-time permanent.................	$7,471,000	$7,586,000	$7,586,000
Other than full-time permanent......	2,993,000	3,040,000	3,040,000
Other personnel compensation........	952,000	972,000	972,000
Total personnel compensation..	11,416,000	11,598,000	11,598,000
Personnel benefits....................	1,719,000	1,751,000	1,753,000
Travel and transportation of persons..	337,000	371,000	371,000
Transportation of things..............	34,000	35,000	35,000
Rent, communications and utilities.....	519,000	542,000	565,000
Printing and reproduction.............	163,000	185,000	190,000

Other services:			
Project contracts	4,696,000	4,484,000	4,586,000
Centrally furnished services	5,671,000	5,671,000	4,672,000
Standard level user charge	364,000	364,000	408,000
Other	2,362,000	2,001,000	2,792,000
Supplies and materials	2,971,000	1,995,000	3,460,000
Equipment	1,104,000	1,200,000	1,200,000
Grants, subsidies & contributions	69,264,000	67,984,000	64,852,000
Total	100,620,000	98,181,000	96,482,000

National Institute of Dental Research

Significant Items in Senate Appropriations Committee Report

Item	Action Taken or To Be Taken
1986 Senate Report	
1. "The Committee was very concerned to learn during the Department's testimony that there appears to be an unusually high frequency of birth defects among nurses who work in operating rooms with dentists. Testimony presented suggested that this might be due to the long-term effects of gaseous anesthetics. The Committee urges NIDR to work collaboratively with the National Institute of Occupational Safety and Health (NIOSH) to address this issue. The Committee wishes to be kept informed of what is accomplished." (Page 68)	1. Representatives from the National Institute of Dental Research (NIDR) and the National Institute of Occupational Safety and Health (NIOSH) have re-examined the research that has been conducted in this area. There have been a limited number of epidemiological studies and animal experiments suggesting that long-term exposure to trace levels of anesthetic gases poses an occupational health hazard to female operating room personnel and dental assistants. Specifically, increased rates of spontaneous abortion and (to a much lesser extent) birth defects have been reported. However, the strength of these epidemiological findings can be questioned because of methodologic problems and they are not consistent with the results from controlled animal experiments. The use of proper waste anesthetic scavenging equipment and procedures, in accord with NIOSH standards, will insure that personnel are not unnecessarily exposed. In order to help further clarify the situation, the NIDR is supporting several grants studying the teratogenesis and other health effects related to long-term exposure to nitrous oxide in animal models. In addition, the NIDR has invited the National Center of Toxicological Research to submit a proposal for an interagency agreement to assess the teratogenicity of selected anesthetic agents used in dental offices.

Item	Action Taken or To Be Taken
1986 Senate Report	
2. "The Committee encourages NIDR to support projects which address the issues involved in improving patient compliance, especially in families with young children. The Committee also urges NIDR to support studies addressing the prevention and reduction of dental pain, especially in younger patients." (Page 68)	2. The NIDR has strongly advocated the routine seeking of dental care beginning in infancy. Institute personnel and grantees have worked with schools, communities and families in preparing children for dental treatment, and have supported disease prevention programs, supplying films and other oral health promotional materials. NIDR-supported behavioral research has shown the effectiveness of a variety of techniques for allaying fear of dental pain in both children and adults. Such interventions include breathing exercises and relaxation therapy, structured pre-treatment information, the use of videotapes, and desensitization programs aimed at reducing fear and anxiety. Basic research on pain has led to new pharmacological and non-pharmacological treatments for dental pain. In addition, new preventive and restorative dental treatments are reducing the need for drilling and other pain-associated dental procedures.

NATIONAL INSTITUTES OF HEALTH
National Institute of Dental Research

Authorizing Legislation

	PHS Act Other Citation	U.S. Code Citation	1986 Amt. Authorized	1986 Estimate	1987 Amt. Authorized	1987 Budget Request
Research and Investigation............	Section 301	42§241	Indefinite	$93,845,000	Indefinite	$92,120,000
National Institute of Dental Research..........	Title IV, Part c	42§288-288c	Indefinite		Indefinite	
National Research Service Awards...........	Section 487	42§288 -1	$244,000,000[1/]	4,336,000	$260,000,000[1/]	4,362,000
Total, Budget Authority....				98,181,000		96,482,000

[1/] This training is shared with other research training programs of the National Institutes of Health; the Alcohol, Drug Abuse, and Mental Health Administration, and the Health Resources and Services Administration.

National Institute of Dental Research

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation [1]
1978	58,811,000	59,728,000	63,747,000	61,728,000
1979	62,039,000	63,841,000	60,000,000	65,213,000
1980	66,484,000	68,318,000	67,000,000	68,303,000
1981	70,060,000	71,206,000	71,083,000	71,114,000
1982	65,672,000 [2]	75,277,000	76,557,000	71,983,000
1983	74,462,000	80,304,000	77,416,000	79,290,000
1984	80,679,000	84,226,000 [3]	84,398,000 [3]	88,674,000
1985	91,096,000	98,451,000 [4]	95,826,000	100,991,000
1985 Proposed Rescission	-166,000			
1986	98,841,000	97,691,000 [5]	103,728,000	103,282,000
1986 Sequester	-4,441,000			
1987	96,482,000			

[1] Reflects enacted supplementals, rescissions, and reappropriations.

[2] Reflects the September amendment; the original request was $74,627,000.

[3] Excludes $3,735,000 in NRSA training programs not considered.

[4] Excludes $4,687,000 in NRSA training programs not considered.

[5] Excludes $4,562,000 in NRSA training programs not considered.

National Institute of Dental Research

Justification

	1986 Appropriation Amount	1986 Available after Sequestering Amount	1986 Revised FTEs	1986 Revised Amount	1987 FTEs	1987 Amount
Diseases of the teeth and supporting tissues...	$52,390	$49,824	---	$49,824	---	$48,154
Disorders of structure, function, and behavior...	15,805	15,442	---	15,442	---	14,917
Dental research institutes...............	7,599	7,272	---	7,272	---	6,367
Intramural research......	20,004	19,135	255	19,135	255	20,303
Research management and support..............	6,870	6,508	74	6,508	74	6,741
Total.............	102,668	98,181	329	98,181	329	96,482

General Statement

The National Institute of Dental Research (NIDR) is the chief Federal agency supporting research on oral health and disease. Major efforts are aimed at improving treatment and ultimately preventing the most prevalent dental diseases, dental caries and the periodontal diseases, as well as oral cancers, herpes virus infections, chronic pain, craniofacial anomalies and other conditions affecting the soft and hard tissues of the orofacial region. These activities entail study of the basic mechanisms of growth, repair and regeneration of cells and structures that are unique to the oral cavity, as well as tissues comparable to other body cells and systems. Thus, dental research today has become a broad-ranging biomedical and behavioral discipline with implications for improving not only the oral health of the American people, but their general health and well-being as well. In carrying out its mission, the NIDR supports extramural research and research training in three major program areas: dental caries and restorative materials; the periodontal diseases, soft and mineralized tissue diseases, nutrition, and dental implants; and craniofacial anomalies, pain and behavioral sciences research. The Institute supports intramural research through eight laboratories and two clinics, both a dental clinic and a pain research unit at the NIH Clinical Center. An Epidemiology and Oral Disease Prevention Program was inaugurated in 1984 to address the need for expanded and updated data on oral conditions and to facilitate the rapid transfer and adoption of disease prevention and oral health promotion measures by the professional and lay public.

Extramural Research, Training, & Center Mechanisms

The NIDR has made use of the wide range of grant support mechanisms and research training and manpower development programs available at the NIH in carrying out its mandate. In addition, the Institute has implemented a unique Dentist Scientist Award appropriate to the special needs of individuals holding the DDS or DMD degree who wish to pursue careers in research. The NIDR has also made innovative use of the Center grant support mechanism to fund basic research at five Dental Research Institutes and Centers and categorical research at specialized dental research centers.

Following the request of Congress, the NIDR has submitted its final report reviewing the Institute's use of research center grants and other large grant mechanisms and stating how such grants will be used in the future. The report reflects broad consultation with the dental community whose advice and opinions were elicited at professional meetings, through letters, and open meetings convened by a special 20-member ad hoc Consultant Panel. The report and recommendations of the Panel, whose members included the Directors of all 5 Dental Research Institutes as well as representatives of the major professional organizations, were endorsed by the NIDR Programs Advisory Committee and the National Advisory Dental Research Council. The NIDR concurs with the philosophy expressed in the Panel report and has developed an implementation plan to carry out 8 of the 9 recommendations presented, deferring, for the time being, a recommendation to develop demonstration research projects. The reasons for deferral were 1) demonstration research is now being conducted under contract and 2) the Institute believes its financial and staff resources should be directed initially to implementation of the principal kinds of research centers and large programs that the Panel has recommended. In essence, the NIDR will continue to use the range of grant mechanisms available, strive for balance in its research portfolio, and ensure that all large grants are awarded through open competition and rigorous peer review. Accordingly, the Institute has issued a request for applications for new Research Centers in Oral Biology (RCOB) where multidisciplinary and interdisciplinary teams of investigators can address a variety of research issues. The first awards in this program will be made in FY 1987.

New Initiative on Oral Health in the Elderly

The NIDR Long-Range Plan, Challenges for the Eighties, FY 1985-89, completed in December 1983, has served as a review of oral health research as well as a blueprint for the future. The plan emphasized the wider scope of dental research and the need to expand concerns from dental diseases in children to all the oral diseases and conditions that affect individuals throughout the lifespan. Toward that end the NIDR has embarked on an interagency collaborative research project on oral health in the elderly. Working with the National Institute on Aging (NIA) and the Veterans Administration (VA), the NIDR has developed a Research Agenda pointing to the needs for research in many areas, including normal oral tissue changes in age, particular oral health problems, the relation of oral health to general health, the delivery of services, new preventive measures, and clinical decisionmaking. The three agencies plan to use the Agenda and supporting documents to develop two-or three-way collaborative research projects that can maximize the use of the talents and research resources unique to each agency.

Plans call for publishing the Agenda early in 1986 and giving widespread notice of its availability to professional groups as well as lay organizations. The NIDR also intends to reach out to the middle-aged segments of the population as an especially appropriate target for new efforts in oral health promotion and disease prevention so that future age cohorts moving into advanced age can maintain their dentition in health and avoid problems characterizing the present cohorts.

Overall Budget Policy

The 1987 budget request for the National Institute of Dental Research is $96,482,000, $1,699,000 less than the 1986 current estimate of $98,181,000.

The National Institute of Dental Research will continue in 1987 to emphasize the importance of research grants and will fund an estimated 110 competing grants.

These levels will be achieved by limiting indirect cost and by negotiating direct costs downward. The request will support 110 competing project grants at an average cost of $115,000. This represents a 9.2 percent increase in direct costs over 1986 and a 13.6 percent reduction from full recommended levels. Historically, these reductions have averaged 3 to 4 percent. The request will support 269 noncompeting project grants at an average cost of $113,000. This represents an 8 percent increase in direct costs over 1986 and a 6.4 percent reduction from full commitment levels. Historically, these reductions have averaged 1 percent.

The request provides $11,790,000 for 16 research centers, a reduction of $1,517,000 from the 1986 estimate for the same number of research centers. Downward negotiations of approximate 11.4 percent will be necessary. This compares with negotiated reductions of 4.3 percent in 1986.

In other research, the request will provide funding for 123 awards at $5,456,000. The funding level for the Minority Biomedical Support Program in 1987 will be $117,000. In addition, the Institute will continue its small grants program in 1987 of $1,135,000 a reduced level of 9.6 percent compared to 1986 of $1,255,000 a reduced level of 4.3 percent, continuing to provide support for meritorious dental research projects. Such projects will continue to stimulate the development of innovative research grants in the future.

The Institute will provide support in 1987 for 42 individual training awards at $1,050,000, and 162 trainees for institutional awards at $3,312,000 for a total of 204 trainees and $4,362,000.

Support for research and development contracts in 1987 will be 34 contracts for $4,586,000.

Funding for intramural research and research management and support will be $20,303,000 and $6,741,000 respectively.

The request excludes $2,768,000 for AIDS, which are under the single AIDS appropriation in OASH. Comparable amounts for 1986 are $684,000 and for 1985 $97,000.

Program Accomplishments

Caries:

Work continues on understanding the multiple mechanisms by which fluoride protects developing enamel and aids in remineralizing early caries lesions. Efforts to reduce the prevalence of caries beyond levels already achieved are emphasizing studies of oral ecology and immunology. Scientists are testing the feasibility of blocking mother-to-infant transmission of Streptococcus mutans, considered the principal cause of tooth decay, by coopting colonization sites in erupting teeth with non-virulent strains. Elimination of the pathogen in the oral cavity of adults is also feasible. Immunological studies are focusing on improving understanding of secretory immunity and studying a variety of candidates for an anticaries vaccine. Public awareness of caries preventive measures appears to be growing as seen in increased use of dental sealants to prevent decay on occlusal surfaces. Two Caries Research Centers are concentrating on ways to protect cemental surfaces of teeth to prevent root surface caries which appears to be an increasing problem in adults.

Restorative Materials:

New adhesive materials and methods of application that will permit bonding of restorative materials to both dentin and enamel are being tested in a 5-year clinical study by NIDR-supported investigators at the National Bureau of Standards. An interagency agreement with the VA will permit comparisons of palladium-based and all-ceramic crown and bridge systems with gold-ceramo-metal alloy systems in studies conducted at 6 VA hospitals. The feasibility of using sealed composite restorations to arrest caries lesions without cavity preparation and without removal of the lesion material is under investigation. Such treatment is unlikely to require anesthetic injection and conserves tooth structure. The sealed composite restorations are being compared to standard amalgam restorations.

Periodontal Diseases:

Studies of relatively rare periodontal diseases are contributing to better understanding of the pathogenesis and immune responses to these diseases. Thus, defective polymorphonuclear (PMN) white blood cells have been shown to be an important factor in juvenile periodontitis(JP), a severe form of periodontal disease that runs in families. The PMN cells fail to migrate rapidly to the sites of infection. This failure has now been attributed to the absence of a single cell surface protein. Lack of this protein in a child in a family with JP might also indicate that the child is at risk for the disease. A newly defined syndrome which affects young children, prepubertal periodontitis, also appears to involve PMN deficits, in this case complete inability of the cells to migrate to the site of infection. Other studies have explored the reasons for higher susceptibility to periodontal diseases in diabetic patients. One study found reduced cellular uptake of ascorbic acid in the cells of diabetic patients compared to normal cells.

Basic research has focused on the steps by which periodontal pathogens are able to adhere to oral tissues or other bacteria and colonize the oral cavity. Specific cell surface components involved in attachment and adherence have been identified and genes coding for the units isolated and cloned, thus paving the way for interventions that could curb these processes. In other studies, investigators have found ways to confound bacterial metabolism. The use of certain sugar analogues led particular species of lactic acid bacteria to the exhaustive repetition of futile cycles in which the organism moved the sugar compound inside the cell, was unable to metabolize it, and exported the compound outside the cell, only to begin the cycle anew.

Soft Tissue Diseases:

Three approaches to controlling herpes simplex virus (HSV) infections are under study. The first approach is prevention through the use of a genetically engineered vaccine composed of an HSV cell surface antigen gene and the vaccinia virus. This vaccine proved effective in protecting mice against HSV 1 and HSV 2 infections in experiments conducted a year ago. Recent experiments--the first to test the duration of a recombinant vaccine--have shown that the mice are still protected. The effects of booster doses also will be tested. The second approach is designed to ameliorate HSV infection. The drug acyclovir has been shown to reduce the frequency of reactivation of genital herpes when given prophylactically on a daily basis. A third approach is aimed at elucidating the processes involved in triggering reactivation. These studies have implicated ultraviolet light as a trigger and are allowing investigators to study the early skin changes that precede overt herpes lesions.

Other research is exploring the possible co-carcinogenic effect of constituents of cigarette smoke and the presence of HSV antibodies in initiating oral cancer. The role of viruses as a factor in the etiology of insulin dependent diabete mellitus (IDDM) also continues to be explored. Previous studies had shown that diabetes could be induced in mice following infection by certain viruses. A patas monkey model of viral-induced diabetes has now been developed in collaboration with NIAID investigators. In related studies, investigators have tested the hypothesis that antigens made to viral agents may cross-react with host cells. In tests using 600 monoclonal antibodies made against 11 different viruses, investigators found that a high percentage (about 4 percent) of these antibodies reacted with specific cells in various human tissues. This kind of "molecular mimicry" may play a role in a variety of autoimmune diseases including IDDM, multiple sclerosis and lupus erythematosis.

AIDS:

Immune studies have shown specific monocyte defects in AIDS patients including chemotactic defects, diminished cytotoxicity for extracellular organisms and a marked reduction in the ability to produce Interleukin-1 (IL-1). Twin studies have also disclosed that monocytes from a twin with AIDS had decreased accessory cell function but that this abnormality could be restored in part by exogenous IL-1 or by replacment with healthy twin monocytes. Findings also suggest that monocytes can be infected with human T-cell lymphocytotrophic virus III (HTLV-III). The NIDR has appointed a Task force on AIDS and conducted an interagency workshop. Recommendations from the Task Force are being used to plan further NIDR AIDS research in immunology, clinical studies and salivary/oral cavity studies.

Craniofacial Anomalies:

The role of enamelins and amelogenins, proteins secreted by ameloblasts during the course of development of tooth enamel is under study, as well as the timing of expression and the regulation of the genes coding for these proteins. Hyaluronic acid molecules, major components of the extracellular matrix of embryonic and regenerating tissues, appear to play a significant part in cell differentiation. The highly charged molecules form a network controlling diffusion of water and providing pathways for cellular migration. Later, they may serve as a scaffolding for cartilage formation. Several clinical studies have compared early versus later repair of cleft palate suggesting that early repair did not inhibit overall facial growth. Furthermore, in patients with cleft palate accompanied by otitis media, early surgery to place tympanostomy tubes (during the first year of life) resulted in improved auditory acuity and consonant articulation compared to later tympanostomy placement.

Pain Control:

Neuroanatomical studies suggest that a particular brain stem nucleus, subnucleus caudalis, is the main terminus for nociceptive (pain) signals from tooth pulp. However, non-pain signals from other orofacial sites may also converge on these neurons, suggesting an explanation for the sensation of spreading pain or referred pain. Other basic studies have identified a new nociceptive pathway in the midbrain which may be involved in the motivational and autonomic nervous system consequences of painful stimulation. Clinical studies in the NIH Ambulatory Care Research Facilty Pain Unit have demonstrated the usefulness of tricylic antidepressants in the treatment of diabetic neuropathies as well as in the treatment of post-shingles pain and atypical facial pain.

Behavioral and Social Science Research:

An epidemiological study of temporomandibular disorders is under way. This study will focus on risk factors, prognostic indicators and the prevalence of specific signs and symptoms of a disorder which has been little understood and subjected to a wide range of treatments. The relationship of stress to particular pain problems is being explored in studies of myofascial pain dysfunction (MPD) syndrome. Pain ratings and stress are evaluated in patients each month and compared with life stress data and personality measures on matched controls.

Epidemiology and Oral Disease Prevention:

A major national survey of the oral health status of adults and of the elderly will be completed early in 1986 providing up-to-date information on the prevalence of coronal and root caries, the periodontal diseases, and other oral conditions in some 20,000 adults seen at workplaces or senior citizen centers. A multi-center collaborative study has just begun in an effort to find differences in microbiologic, immunologic, or biochemical parameters among older adults with and without a history of periodontal disease. Successful development continues of a controlled-release system for low-cost administration of topical fluoride and other preventive agents. A six-month clinical trail in children has been completed and new trials will include studies of the effectiveness of the device in preventing caries in high-risk cancer patients who suffer dry mouth secondary to head and neck radiation therapy.

Acquired Immune Deficiency Syndrome

Funding for Acquired Immune Deficiency Syndrome (AIDS) was $97,000 in FY 1985, $684,00 in FY 1986, and planned funding for FY 1987 is $2,768,000. AIDS was first reported in the U.S. in 1981 and since then has had a significant impact on the nation's health and health policy. The extremely high mortality rate and the annual doubling of AIDS cases has prompted a massive marshaling of fiscal and human resources to counteract the advances of this insidious disorder. A number of specific oral lesions have now been associated with AIDS and in some cases may precede the frank clinical picture of AIDS. Thus certain of these disorders could serve as predictive or diagnostic markers for AIDS itself. The level of certain proteins or other components of saliva may also change during the course of development of AIDS. Salivary components of particular interest in this regard are the histidine-rich proteins (HRP). These proteins are known to inhibit the germination of Candida albicans. Since oral candidiasis often represents a critical stage in the development of AIDS, the salivary levels of HRP may have important diagnostic and predictive values in this serious condition.

NIDR intramural scientists have been studying monocyte immunology and biochemistry to understand the contribution of this cell to the pathogenesis of AIDS. Initially, the investigators found that monocytes show chemotactic defects, thereby providing in part a very plausible explanation for the reduced inflammatory cell response and, in particular, the absence of granulomatous reactions in AIDS. These investigators have gone on to show reduced monocyte cytotoxicity for extracellular organisms, possibly through diminished oxygen reactive intermediate generation. Recently, they also discovered a marked reduction in the capacity of AIDS monocytes to produce Interleukin-1(IL-1), a key monocyte product involved in immunoregulation. In an additional series of studies using cells from twins in which one twin had AIDS while the other did not, NIDR investigators documented decreased accessory cell function by monocytes from the twins with AIDS. Equally important, this abnormality could be partially restored by exogenous IL-1 or replacement with healthy twin monocytes. Also, in surface antigen studies monocytes were shown to be hyperactivated, although suboptimally functional. Most recently, the same investigators have accumulated preliminary data which demonstrates that monocytes can be infected with HTLV-III, likely accounting for their depressed functions and indicating that monocytes may serve as a reservoir cell for the virus in the host. Finally, these investigators also are identifying infections causing disease in the oral-gastrointestinal tract in patients with AIDS.

The NIDR has established an AIDS Task Force to advise the Institute on AIDS research, and an interagency workshop was held in November 1985. In addition to the ongoing studies mentioned above, new recommendations have been formulated and implementation begun.

Among the projects being considered for 1987 are the following:

o Document the natural history of oral changes in relation to the development of AIDS and as they change over time. Identify the earliest oral changes associated with AIDS as an aid to diagnosis and as a means of permitting early treatment and counselling.

o Document the frequency of occurrence of the AIDS virus in salivary gland secretions, whole saliva, and gingival crevicular fluid. Examine changes in the oral microflora that may occur in relation to the development of AIDS. Determine the presence in the oral cavity of microorganisms associated with opportunistic infections and malignancies in AIDS patients and develop effective measures for their elimination or control.

o Test various lines of Kaposi sarcoma cells for invasiveness. Building on ongoing work on tumor cells, subcultures of Kaposi invasive cells will be developed to determine if they represent a more malignant cell line. Additionally, various chemotherapeutic agents which interfere with cellular migration will be tested as possible adjuncts to conventional therapy.

o Extend studies for the treatment of the chronic pain experienced by AIDS patients utilizing controlled clinical trials with amitriptyline and other tricyclic antidepressant drugs. The two most common causes of chronic pain in AIDS both relate to injury to the peripheral nervous system. Peripheral neuropathy and herpes zoster each occur in 5-10 percent of AIDS patients. There is little available data from controlled studies to guide analgesic treatment of patients with neuropathic pain.

National Institute of Dental Research

Diseases of the Teeth and Supporting Tissues

Public Health Service Act, Title IV, Parts C and I

1987 Authorization: Indefinite:

Budget Authority:

1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987	Increase or decrease
$52,390,000	$49,824,000	$49,824,000 (FTEs: --)	$48,154,000 (--)	-$1,670,000 (--)

Purpose and Method of Operations

The purposes of these activities are to increase information on the etiology, pathogenesis, treatment and prevention of dental caries and to develop improved restorative materials and devices for the prevention and treatment of a range of oral diseases; to develop new knowledge on the cause, pathology, diagnosis, treatment and prevention of periodontal diseases--the major cause of tooth loss in adults--so that the natural dentition can be maintained throughout life; to investigate the causes and methods of preventing and treating oral soft tissue diseases such as canker sores, herpes labialis infections (fever blisters or cold sores) and oral cancer; to develop new knowledge of relationships between nutritional factors and oral health or disease; and to improve understanding of the role of salivary secretions in preventing oral disease. These objectives are pursued through the use of research grants and research centers, contracts, research training, and research career awards.

Rationale for the Budget Request

The 1987 request of $48,154,000 for this activity represents a decrease of $1,670,000 below the 1986 level. The program plans, along with expected accomplishments, are as follows:

Dental Caries

Data obtained from a national survey conducted by the National Institute of Dental Research (NIDR) in 1979-80 showed a dramatic decline in the prevalence of dental caries (tooth decay) in school children compared to results from a survey carried out by the National Center for Health Statistics in 1971-73. The results are subject to various interpretations with implications for future prevention and treatment efforts. The findings also point to the need for periodic evaluations of disease status in the population in order to maintain appropriate prevention and treatment programs or develop new ones.

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More than a third of the Nation's school children were completely caries free in the NIDR survey. To achieve even higher levels of disease prevention it is critical to know whether the decline in caries prevalence is continuing and whether there are geographical or demographic pockets in which disease rates remain high. While the decline has been attributed largely to community water fluoridation and expanded use of fluoride in other forms, other factors could be involved. For example, the decline in caries might be associated with the disappearance or lessened virulence of the chief causal microorganism (*Streptococcus mutans*). Scientists are currently examining the effect of dietary substances (including sweeteners and fluoride) and the widespread use of antibiotics on the ability of *S. mutans* to survive in the mouth.

There is clinical evidence to suggest that individuals become infected with *S. mutans* in infancy and that transmission between adults is infrequent. Scientists therefore are testing the feasibility of blocking mother-to-infant transmission of *S. mutans*. This might be accomplished by coopting *S. mutans* colonization sites in erupting teeth with non-virulent strains of this species. Investigators also are exploring the possibility of eliminating all *S. mutans* in the adult mouth at one time, a technically feasible procedure which might also result in long-term avoidance of infection.

If epidemiologic studies reveal that *S. mutans* and dental plaque persist in individuals even though caries is not occurring, the reason may be that tooth enamel has been strengthened against bacterial acids. Laboratory studies have shown that fluoride has profound effects on the solubility of hydroxyapatite, the mineral component of tooth enamel. The anti-caries effects of fluoride seem easily explained by such effects on hydroxyapatite. Therefore, scientists continue to study the dynamics of enamel demineralization and remineralization, particularly as influenced by fluoride, in the hope of developing yet improved means of preventing decay or enhancing remineralization.

An interesting question arising from the observed low prevalence of caries in school children is what happens in maturity? Are the tooth surfaces that are surviving intact more or less vulnerable to caries later on in life? To find out, the Institute is currently completing a survey of the oral health of working adults and the elderly. Data collected will document the prevalences of coronal and root surface caries, as well as other oral conditions. There is some evidence that caries of root surfaces--involving pathogenic microorganisms other than *S. mutans*--will be an increasing problem as individuals retain teeth to older ages. Thus, considerable research is now focusing on ways to protect the relatively soft cemental surfaces of exposed tooth roots. Two Specialized Centers for Caries Research are studying this aspect of the disease.

The goal of complete eradication of dental caries is not likely to be achieved unless preventive regimens are simple to use, safe, inexpensive and in other ways attractive to the public. Toward those ends, the Institute is supporting basic research on immunology and oral ecology systems. The research includes studies to elucidate the mechanisms by which gut-associated lymphoid tissues respond to microbial antigens and form immunoglobulins that are released in the mouth where they can react with oral microorganisms. Research is aimed at ways to stimulate and direct the activity of this important but poorly understood immune defense mechanism. The research also includes studies to assure the safety of vaccine immunogens based on components of the S. mutans cell wall. Candidate molecules are being purified using gene and antibody cloning techniques, assessed for immunogenic potency and exhaustively screened for possible deleterious reactions with host tissues. In further efforts to achieve potent but completely safe immunogens, scientists are planning to synthesize and test analogs of the antigenic sites of S. mutans antigens. Other investigators are using recombinent DNA techniques to develop non-cariogenic strains of S. mutans to replace the virulent strain. It is encouraging to report that tests already have established that properly modified strains soon dominate wild-type S. mutans and persist for long periods.

Dental caries, a once rampant disease among children, has abated in the United States. Nevertheless the disease remains active in many individuals throughout life. New and more powerful tools are being developed to control the tooth-destructive properties of the causal microorganism, to eradicate it from the mouth, and to prevent its transmission.

Restorative Materials

There is a continuing need for materials to repair oral tissues and restore function and appearance. Research on the materials is in six categories: 1) restorative filling materials; 2) bonding agents, adhesive coatings, and cements; 3) intraoral prostheses for replacing missing teeth and other oral tissues; 4) materials and techniques for improved root canal therapy; 5) diagnostic equipment and devices to improve dental care; and 6) new and improved restorative materials for prevention. Examples of current research are given below.

Investigators at the Paffenbarger Research Center at the National Bureau of Standards, American Dental Association Health Foundation, are conducting a five-year clinical study to determine the biocompatibility, durability and feasibility of adhesive bonding techniques applicable to both dentin and enamel surfaces. The major objectives include: 1) determining the feasibility of the technical procedure under clinical conditions; 2) assessing patient acceptability of the use of these materials to mediate durable long-term retention of composite restorations in the absence of cavity retention forms ("dovetail, undercuts," etc.); 3) judging esthetic characteristics of these materials over time, when applied under clinical conditions; and 4) observing human pulp responses and other indicators of biocompatibility.

The NIDR has awarded an interagency agreement to the Veterans Administration Medical Center at Ann Arbor, Michigan to conduct a multi-center clinical evaluation of alternative crown and bridge systems. Two commercially available palladium-based alloys and two all-ceramic systems are being compared with a gold ceramo-metal alloy to determine the clinical quality, safety, and predictability of restorations fabricated with these alloys, as well as the cost-effectiveness of these systems. The six VA medical centers participating in this cooperative study program are in Buffalo, NY; Pittsburgh, PA; Allen Park, MI; Ann Arbor, MI; San Diego, CA; and San Francisco, CA.

Scientists are conducting studies to evaluate the interactive effect of metal and porcelain properties and prosthesis design on transient and residual stresses which develop in metal-ceramic crown and fixed partial dentures during fabrication, as well as the influence of simulated intraoral forces on the residual stress distribution in porcelain veneers. Investigators believe that stresses induced in porcelain veneers increase the risk of costly remakes and of trauma to patients due to premature failure of these restorations. They also believe that thermal contraction incompatibility of alloys and porcelains is a primary cause of immediate failure during fabrication and may cause delayed failure under superimposed intraoral stresses. Because of the complexity of stress states which result from the multitude of prosthesis geometries, researchers have been unable to agree on criteria to discriminate compatible from incompatible metal-ceramic systems. This study is designed to define compatibility on the basis of both transient and residual stress.

Another research group is determining the feasibility of using a sealed composite restoration to arrest caries without cavity preparation and without removal of the carious lesion. The only manipulation of the tooth is to bevel the enamel around the opening of the natural cavity at the aperture of the carious lesion. The minimal tooth preparation usually does not require any anesthetic injection and conserves tooth structure. The conservatively sealed composite restorations are being compared with conservatively sealed amalgam restorations and with standard Class I amalgam restorations. This research could lead to very significant benefits in clinical practice.

Periodontal & Soft Tissue Diseases

This program supports research on the cause, pathology, diagnosis, treatment and prevention of periodontal diseases and oral soft tissue diseases such as canker sores, herpes labialis infections (fever blisters) and oral cancers. In addition, the program supports studies of the relationships between nutritional factors and oral health or disease and the role of the salivary glands and secretions in maintaining oral health and preventing disease. These objectives are pursued through research grants, research center activities, contracts, institutional fellowships, individual fellowships and research career awards.

Periodontal Clinical Syndromes

Studies of severe but relatively rare periodontal diseases have identified the polymorphonuclear (PMN) white blood cell as a critical host defense cell. In juvenile periodontitis, for example, PMN cells fail to migrate rapidly to sites of infection. A recent study suggests that this chemotactic defect may be due to the absence of a single protein (P110), normally present on the surface membranes of the cells. The use of monoclonal antibodies to P110 should enable investigators to isolate this protein and determine its role in chemotaxis. The investigators also intend to use the protein as a genetic marker, since juvenile periodontitis occurs in families. A cooperative effort to study the genetics of the disease also has been initiated. The research subjects include 247 people in 27 families. Preliminary data analysis suggests that an autosomal recessive mode of inheritance may be involved.

A newly defined syndrome called prepubertal periodontitis has been described. This is an acute inflammation of the gingiva with gingival proliferation, cleft formation and recession. Onset occurs in children about 4 years of age who develop rapid alveolar bone destruction. These children also have otitis media and other infections. The polymorphonuclear cells of these patients are unable to migrate to infected tissues. Normally, PMNs reach distant sites by first adhering to, and then working their way through the walls of the small blood vessels to reach sites of tissue damage. The PMN cells of these children cannot adhere to the blood vessel walls and escape to sites of injury. To show that the defect is cellular, investigators injected PMN cells from normal individuals into the circulation of affected patients. The transplanted cells were able to adhere to blood vessel walls and migrate to the gingival tissues. The inability of the defective cells to adhere to blood vessel walls has been traced to abnormalities in two glycoproteins on the surface of the PMN. According to evidence from other laboratories, these glycoprotein abnormalities are due to a single gene defect transmitted as an autosomal recessive trait.

Diabetic Periodontitis

Recent research indicates that both insulin dependent diabetes mellitus (IDDM) and noninsulin dependent diabetes mellitus (NIDDM) increase an individual's susceptibility to periodontal diseases. In one study, investigators completed a 3-year follow-up of 200 children with IDDM noting that: 1) Severe gingivitis appeared at age 11 and increased with age; 2) Periodontitis with alveolar bone loss was found in 20% of 100 IDDM patients between 13 and 18 years old, while there was virtually no evidence of alveolar bone loss in unrelated or sibling age-matched controls.

In a study of Pima Indians (where the prevalence of IDDM is high) investigators examined more than 1600 individuals from 5 to 90 years old. The most significant oral finding was that 32% of the diabetics had lost all of their teeth, while less than 2% of the non-diabetic group had lost their teeth. Moreover, in the age range of 15 to 55, diabetic subjects who retained teeth showed greater severity of periodontal disease than nondiabetics. The greater severity of periodontitis in the diabetics was not related to amount of plaque or calculus, to sex or other demographic variables examined, but did seem related to glucose tolerance measurements.

Evidence that the diabetic state may cause a local tissue deficiency of ascorbic acid was developed in a study assessing the uptake of C14-labelled ascorbic acid by normal and diabetic human cells. Since ascorbic acid is known to share a common cellular transport system with glucose, the investigators reasoned that high levels of glucose in the blood might exert a competitive inhibition effect and impair the transport of ascorbic acid into cells. Their experiments support this hypothesis. Expansion of these studies should lead to an understanding of the mechanisms that lead to the increased periodontal disease susceptibility of diabetics and to better control of their complications.

Immune Response in Periodontal Diseases

To determine whether lowered immune responsiveness is associated with acute necrotizing ulcerative gingivitis (ANUG), investigators studied patients with ANUG from a population of homosexual men at risk of developing Acquired Immune Deficiency Syndrome (AIDS). The normal prevalence of ANUG is said to be less than 1%, but this group showed a prevalence of more than 9%. Blood samples from these patients showed low numbers of T4 (helper lymphocytes) and normal numbers of T8 (suppressor lymphocytes) so that the T4/T8 ratio was 0.54, instead of 2.0-3.0. Thus, lowered systemic immunity was associated with ANUG.

Three putative periodontal pathogens *Actinomyces viscosus* (*AV*) *Bacteroides gingivalis* (*BG*) and *Actinobacillus actinomycetemcomitans* (*Aa*) have been studied for their capacity to alter host immune responses by effects on B lymphocytes and on T lymphocyte subsets. Cultures with *AV* resulted in a higher percentage of T helper cells and a higher T4/T8 ratio (>3.0) when compared to controls (2.0), and a higher percentage of B cells. In contrast, cultures with *BG* and *Aa* resulted in higher percentages of suppressor T cells and a lower T4/T8 ratio. Thus two important periodontal pathogens (*Aa*. and *Bg*.) exert a suppressor effect on the cellular immune response.

To determine whether the humoral immune system can provide protection against periodontal diseases, investigators have actively and passively immunized rats against the *Aa*. organism. Subsequently, the animals were infected with *Aa* and periodontal bone losses were measured. High levels of specific antibody to *Aa* in the serum of the test animals did not provide protection. To test whether the cellular immune system was protective, the investigators made preparations of T helper (TH) and T suppressor (TS) rat lymphocytes specifically sensitized against *Aa*. Preparations of either the TH or TS cells were then injected into rats which were subsequently infected with viable *Aa* organisms. Recipients of the *Aa* antigen-specific TH cells showed less periodontal bone loss than controls. On the other hand, recipients of the *Aa* antigen-specific TS cells showed greater bone loss than controls. These results support the concept that immune responses can exert either protective or destructive effects.

Oral Cancer

Recently published studies on the interaction between viruses and chemicals in the etiology of cancer have indicated that patients with oral cancer have increased herpes simplex type 1 (HSV-1) serum antibodies and that cigarette smokers also have higher levels of these antibodies. The investigators hypothesize that a co-carcinogenic effect results from interaction between HSV-1 and some smoke constituents, causing malignant changes in the oral epithelial cells. To test this hypothesis, the investigators are carrying out experiments in mice using smoke condensates and related chemical carcinogens, methylcholanthrene (MCA) and dimethylbenzanthracene (DMBA) together with HSV-1. Preliminary studies have shown that the administration of MCA and HSV-1 in combination resulted in a five-fold increase in tumor incidence in mice. However, when DMBA and HSV-1 were administered in combination, the result was 100% mortality. Future plans include an attempt to inhibit the co-carcinogenic effect of HSV-1 and smoke constituents using selected drugs.

Salivary Glands

Since bacterial plaque is the key etiological factor in dental caries and periodontal diseases, studies are being conducted to understand how bacteria adhere to tooth surfaces. In these studies scientists are determining the structural and functional relationships of certain salivary proteins believed to be involved in early plaque formation. Amino acid sequence determinations and structural studies of proline-rich proteins in saliva indicate that these proteins are poorly susceptible to proteolytic cleavage and therefore may be expected to remain intact in developing plaque.

Nutrition

Preliminary findings indicate that dietary zinc interferes with the intestinal absorption of calcium. This observation is significant for elderly individuals who may be taking daily medications with a high zinc content. To determine optimal dietary levels, investigators gave varying amounts of calcium and zinc to human subjects and to animals. The results showed that with a calcium intake of 800 mg per day, high zinc intake did not reduce the absorption of calcium, but when the calcium intake was lowered to 200 mg per day, the same high zinc intake caused a severe reduction in calcium absorption. These findings suggest that elderly individuals who take medicines with a high zinc content may have to increase calcium intake to lower the risk of developing osteoporosis. These studies will be continued.

Dental Implants

A long-term clinical trial of artificial dental implants continues. In this study, blade-implant-supported bridges are being compared in efficacy and safety to nonimplant-supported cantilever bridges. So far, the longest follow-up time for any patient in the study is 3 years, but all patients have been followed for a least 18 months. Results to date indicate no differences in mobility and bone loss between the implant-supported and the cantilever bridges, but pocket probing and gingival health measurements were more favorable in the implant-supported bridges.

Smokeless Tobacco

Recent reports of increased use of smokeless tobacco, especially among teenagers, have prompted the Surgeon General, PHS, to appoint an advisory committee and three technical support groups whose members include NIDR staff. The NIDR, the National Cancer Institute and the office of Medical Applications of Research, NIH are jointly sponsoring a Consensus Development Conference in January 1986 to address the health concerns of smokeless tobacco use. In addition, one of the technical support groups recently concluded a review of the current literature on the non-cancerous oral effects of smokeless tobacco use. They concluded that additional human and animal studies are needed to determine the oral effects of smokeless tobacco use. Their recommendations, along with those developing from the consensus conference, will form the basis for the NIDR research efforts in this important area.

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987
Caries and restorative materials..	$23,198,000	$22,239,000	$22,239,000	$21,603,000
Periodontal and soft tissues diseases..	29,122,000	27,585,000	27,585,000	26,551,000
Total..............	52,320,000	49,824,000	49,824,000	48,154,000
Res. proj. grants				
Number	294	292	292	280
Amount	34,595,000	32,862,000	32,862,000	31,521,000
Res. centers				
Number	8	8	8	8
Amount	5,401,000	5,169,000	5,169,000	4,663,000
Other research				
Number	101	99	99	91
Amount	4,674,000	4,473,000	4,473,000	4,518,000
Training				
Number	139	132	132	134
Amount	2,964,000	2,836,000	2,836,000	2,866,000
R & D contracts				
Number	35	33	33	34
Amount	4,686,000	4,484,000	4,484,000	4,586,000
Total				
Number	577	564	564	547
Amount	52,320,000	49,824,000	49,824,000	48,154,000

National Institute of Dental Research

Disorders of Structure, Function and Behavior

Public Health Service Act, Title IV, Parts C and I

1987 Authorization: Indefinite.

Budget Authority:

1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987	Increase or decrease
$15,805,000	$15,442,000	$15,442,000 (FTEs: --)	$14,917,000 (--)	-$525,000 (--)

Purpose and Method Of Operations

The purposes of activities in these areas are: 1) to conduct research on the cause, prevention, and treatment of congenital anomalies such as cleft lip and cleft palate; to conduct research on malocclusion of the teeth and jaws and to study disfigurements acquired through accidents or surgical procedures, so that these conditions can be prevented and treated more effectively; 2) to increase understanding of the mechanisms underlying dental and orofacial pain and to develop improved methods for prevention, diagnosis, and treatment of oral pain problems; and 3) to determine how human behavior influences the risk for oral disease as well as disease prevention, diagnosis, and treatment. These objectives are pursued through use of research grants, contracts, research training and research career awards.

Rationale for the Budget Request

The 1987 budget request of $14,917,000 represents a decrease of $525,000 below the 1986 level. The Program plans for 1987 along with expected accomplishments, follow:

Craniofacial Anomalies

Many congenital craniofacial malformations are attributable to abnormal cellular differentiation. During the formation of dental enamel, for example, epithelial cells differentiate to form ameloblasts. These cells secrete at least two specific types of proteins, enamelins and amelogenins. These proteins play a critical role in the formation of enamel, the hardest substance in the body. Enamelin binds calcium ions and initiates growth of calcium apatite crystals to form ribbon-like structures. The enamel matures by increasing the density of the mineral phase and by removing water and protein. It has been proposed that the amelogenins, which are hydrophobic, remove water and facilitate crystal growth. The genes coding for certain enamelins and amelogenins have now been isolated and characterized. Understanding the expression of these and related genes will be helpful in developing diagnostic procedures and ultimately devising treatments for hereditary diseases of enamel such as amelogenesis imperfecta.

Hyaluronic acid (HA) is a major component of the extracellular matrix of embryonic and regenerating tissues. It has remarkable hydrodynamic and adhesive properties that may explain its role in cellular differentiation, morphogenesis and wound healing. Highly charged HA molecules form a network which controls diffusion of water and other extracellular matrix molecules, provides pathways for cellular migration and may direct anatomical changes in shape. Studies of developing chick limbs may further elucidate these processes. It appears that as cells differentiate there is increased HA binding associated with an increase in specific HA-cell surface receptors. Lack of HA binding in undifferentiated cells could permit cell proliferation and movement, while increased binding due to receptor development could facilitate condensation and provide a scaffold for cartilage formation. Research also will be expanded on bone growth-inducing factors, such as bone morphogenetic protein (BMP). This protein can be isolated in minute amounts from human and bovine bone and stimulates new bone production in vivo. BMP may behave like a hormone initiating a cascade of events including perivascular mesenchymal cell migration and differentiation and leading to cartilage and bone formation. When BMP was placed across a gap in resected dog ulna, it induced cartilage and woven bone formation in four weeks. The resorbed cartilage and woven bone were replaced by lamellar bone and marrow, with union of the bone occurring within 12 weeks. Experimental use of BMP implants in craniofacial defects in rats, dogs and monkeys and in tibial and femoral defects in human patients indicates a promising use of this factor in the treatment of congenital and acquired craniofacial defects.

Studies with animal models and clinical trials with human patients are being conducted to evaluate the effectiveness of surgical procedures to correct congenital anomalies such as maxillomandibular imbalance and clefts of the lip and palate. If adult monkeys are fitted with appliances which prevent the jaws from closing normally, marked changes occur in the configuration of the joints and muscles of mastication. On the other hand, the jaws and muscles of juvenile monkeys adapt to the same type of appliance rapidly and return to their normal growth patterns. These variations in response emphasize the need to use different approaches with adult and juvenile orthodontic patients.

The timing of the surgical repair of cleft palate has been controversial because of concerns of the effects of surgery on orofacial growth and function. Contrary to expectations, early repair of surgically created cleft palates in beagle dogs did not inhibit overall facial growth as assessed when the dogs were fully grown. A similar conclusion was reached from a human study. Comparison of serial head films from surgically treated cleft palate children with noncleft craniofacial growth patterns, showed that compensatory growth occurs: the anatomical deviations present during childhood had largely disappeared by the time the patients had become adults.

Cleft palate is almost always accompanied by otitis media for which the only effective treatment is myringotomy with insertion of tympanostomy tubes. The persistent middle-ear effusions of infants with untreated cleft palate are associated with conductive hearing losses of varying degrees. The optimum timing of surgical tube insertion to relieve the middle ear disease is being studied. In one recently completed cross-sectional study, children who underwent tympanostomy tube placement within the first year of life were compared with children who received placement at later ages. The clefts of children from both groups had been repaired between 1 and 2 years of age. Differences favoring the early treated group were found regarding auditory acuity and consonant articulation, but not regarding otologic status, verbal or performance IQ or emotional status. A longitudinal study under way should amplify these findings. Support of these and other long-term studies is essential to evaluate different surgical procedures and schedules for the correction of clefting and other craniofacial anomalies.

The timing and sequence of events governing tooth eruption are the subject of ongoing studies expected to provide much needed information on local control of bone metabolism. The eruption of the third permanent premolar in beagle dogs is the model under study. The investigators have found that the tooth itself does not contribute to eruption. The eruption process proceeds normally even when the growth of the tooth roots is prevented surgically or when the tooth crown is removed or replaced with inert materials. Also, resorption of bone in the anticipated eruption pathway still occurs when tooth movement is prevented by transmandibular wires. What does appear to be essential for eruption is the presence of the tooth follicle. Mononuclear cells line the adjacent alveolar bone surface before and during tooth eruption and their number increases in the follicle as osteoclasts increase in the crypt, suggesting that the follicle coordinates the local metabolic activities required for eruption. These findings may lead to methods of controlling abnormal tooth eruption patterns and new orthodontic procedures to facilitate tooth movement.

Pain Control and Behavioral Research

Anticipation of pain prompts many Americans to delay or avoid needed dental care, thereby reducing opportunities for effective prevention or early detection and treatment of oral disease. Additional millions of Americans suffer costly, disabling chronic orofacial pain conditions, with an estimated 20-25% of all reported chronic pain conditions occurring in the head or orofacial region. Thus, it is not surprising that dental investigators are leaders in research on the causes and control of pain in the teeth and surrounding orofacial tissues, and are making major contributions to basic knowledge concerning both acute and chronic pain.

Extensive single-cell recordings of neuronal activity within the subnucleus caudalis of the brainstem during both electrical and thermal canine tooth pulp stimulation suggest that caudalis neurons may be the essential brainstem element in the central transmission of nociceptive (pain) signals from tooth pulp. In addition, it appears that nerve signals occasioned by a variety of non-painful stimuli such as touch or pressure may converge on neurons in the caudalis. This could explain the sensation of spreading pain or pain referred to non-damaged sites within the craniofacial region. Both high threshold jaw and tongue muscle and skin/mucosal sensory (afferent) neuron endings have been found to converge preferentially on caudalis nociceptive transmission neurons. For example, recordings of 470 single neurons in the caudalis revealed that over 60% of these neurons were excited both by jaw and tongue muscle and skin/mucosal afferent inputs. A majority of these same convergent nociceptive neurons in caudalis were also excited by canine or premolar tooth pulp stimulation and by cutaneous or muscle afferent inputs from the neck. These neurophysiological studies will be expanded in order to determine more fully the neural mechanisms underlying the transmission of both superficial and deep craniofacial pain. Further, such studies should help to elucidate the mechanisms which underlie referred pain and account for the clinically observed phenomenon of difficulty in localizing pain within the orofacial region.

In other studies, post-surgical pain following extraction of third molars will be used as a model for studying the effects of analgesic mechanisms, including the endogenous endorphinergic system. Studies using this model have confirmed that the morphine antagonist, naloxone, can block so-called "placebo" analgesia in some patients. These studies also have shown interesting differences in the effects of tricyclic antidepressants (TCAs) on chronic as opposed to post-surgical pain. TCAs have been commonly used in the treatment of chronic pain and show direct analgesic effects. Results with post-surgical pain, however, suggest that neither desipramine nor amitriptiline has direct analgesic effects. However, desipramine (a relatively selective noradrenaline uptake-inhibitor) shows a synergistic effect with morphine in reducing the magnitude and duration of pain reduction following morphine injection, while amitriptyline (a relatively selective serotonin uptake-inhibitor) shows no such effect. Continuing work will evaluate the properties of interaction between TCAs and opiate analgesics in both acute and chronic pain.

An epidemiological study of temporomandibular disorders has recently been initiated which will focus upon risk factors, prognostic indicators, and the prevalence of signs and symptoms associated with this disorder. This will be a case-control study drawing upon a large Health Maintenance Organization sample. The project is expected to fill a serious void in current understanding of this perplexing, chronic pain condition for which treatment costs have been rising exponentially.

Several chronic orofacial chronic pain conditions appear to be related to psychological factors and life stress. This appears to be true of myofascial pain dysfunction (MPD) syndrome, involving symptoms of facial muscle pain. In ongoing research, relationships between pain ratings and stress are being evaluated in MPD patients each month. These are then compared with life stress data and affective and personality measures obtained on matched controls. Preliminary findings indicate that MPD patients show considerable variability across time in their pain reports and that pain ratings tend to be highly correlated with recent undesirable life events. MPD patients also tend to be characterized by significantly higher levels of demoralization and depression than noted in the control subjects.

Behavioral research also will be directed toward improving the prevention and treatment of oral diseases. For example, an ongoing study is assessing psychosocial functioning in a large sample of orthognathic surgery patients. In this project, questionnaires and a comprehensive psychometric test battery were administered at various intervals before and after surgery. The same measures were also administered to physically comparable groups of patients who chose to have orthodontic treatment only, or who elected to have neither orthodontic treatment nor surgery.

At initial assessment (6-12 months pre-treatment) patients who eventually elected orthognathic surgery reported, as a group, lower facial body image scores than did those who chose to receive orthodontic treatment only or no treatment at all. However, by the 6 month follow-up assessment the surgery patients showed the highest average self-reported facial body image. Patients with unrealistically positive expectations of surgical outcomes were found to report greater dissatisfaction after surgery.

The available findings have major significance for improving presurgical patient preparation and post-surgical management of individuals experiencing orthognathic surgery to ameliorate dental malrelations. Additional research to improve patient preparation for dental or orthognathic procedures is planned.

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Estimate	1987
Craniofacial anomalies, pain control, and behavioral studies.	$15,805,000	$15,442,000	$15,442,000	$14,917,000
Total	15,805,000	15,442,000	15,442,000	14,917,000
Res. projects grants				
Number	103	105	105	99
Amount	12,344,000	12,129,000	12,129,000	11,723,000
Res. centers				
Number	3	3	3	3
Amount	905,000	866	866	760
Other research				
Number	32	28	28	32
Amount	958,000	917	917	938
Training				
Number	73	72	72	70
Amount	1,598,000	1,530,000	1,530,000	1,496,000
R & D Contracts				
Number	-	-	-	-
Amount	-	-	-	-
Total				
Number	211	208	208	204
Amount	15,805,000	15,442,000	15,442,000	14,917,000

National Institute of Dental Research

Dental Research Institutes

Public Health Service Act, Title IV, Parts C and I

1987 Authorization: Indefinite.

Budget Authority:

1986 Appropriation	Available after Sequestering	1986 Revised Estimate	1987	Increase or decrease
$7,599,000	$7,272,000	$7,272,000	$6,367,000	-$905,000
		(FTEs: --)	(--)	(--)

Purpose and Method of Operations

The purpose of this activity is to provide institutional and project support for the study of a broad range of basic and clinical research problems relevant to oral health and disease in a setting which utilizes the full resources of a university.

Rationale for the Budget Request

The 1987 budget request of $6,367,000, for this activity represents a decrease of $905,000 below the 1986 level.

Following discussions with relevant Congressional bodies, the NIDR has completed a comprehensive evaluation on its Dental Reseach Institutes and Centers (DRICs). A special report on this effort requested by Congress has now been provided. Based on the recommendations that emerged from this evaluation, the Research Centers in Oral Biology (RCOB) Program is scheduled to be implemented in FY 1987. This RCOB Program will be based on applications received in open competition and subjected to uniformly rigorous peer review. Research emphases in the RCOB Program will be on basic science areas relevant to oral diseases and disorders with appropriate applied research extensions. Multidisciplinary approaches and collaborative efforts will be strongly encouraged.

The NIDR is currently supporting five Dental Research Institutes, five Periodontal Disease Research Centers and three Caries Research Centers for a total of 13. NIDR is planning to support three additional Centers during FY 1986 bringing the total number of Centers to 16.

Scientific progress in the Dental Research Institutes and Centers continues. Examples of their accomplishments include the following:

Studies on how the body's own immune system may contribute to pathogenicity have led to the development of a model of immune-mediated cytotoxicity which may play an important etiologic role in the development and persistence of periodontal disease. This model of antibody-dependent cell-mediated cytotoxicity directed to host tissues by bacterial pathogens and bacterial components utilizes all those components of host immunity present in healthy individuals (effector cells and antibacterial antibodies). The degree of tissue destruction depends on the amount and types of microorganisms present in the gingival crevice. Ongoing studies of lymphocyte activation and immunoregulatory mechanisms point to the uniqueness of many of the oral microorganisms as immunological stimulants in this pathogenic process.

An improved multimembrane method for assessing abnormalities in chemotaxis of blood monocytes and neutrophils has been characterized and used in studies of various early-onset forms of peridontitis. Based on studies of 133 patients and a large group of control individuals, it was concluded that most if not all patients having prepubertal, juvenile, or rapidly progressive periodontitis manifest defects in the function of neutrophils or monocytes, or both.

Important studies also have been conducted to elucidate mechanisms of regulation of bone deposition and resorption. The data implicate insulin-like growth factors in the stimulation of skeletal growth. These factors induced anabolic effects on both bone cell and bone organ cultures. Receptors for both factors were demonstrated on bone-forming cells. It appears that these factors exert their effects on skeletal growth by direct action on cellular transcription or translation processes.

Previous studies have characterized a skeletal growth factor that acts as a mitogen for bone cells. It has been demonstrated that this factor is involved in controlling bone metabolism at the local level. With regard to bone resorption, methods have been developed for the isolation of pure populations of osteoclasts. In addition, investigators are generating monoclonal antibodies to the surface components of these cells.

Calcification of hard tissues is known to be regulated by a variety of local and systemic factors. The mechanism of mineralization at the biochemical level and its control by these diverse factors remain obscure. Innovative analytical tools have been developed for studying the role of cell metabolism in calcification. Using these methods, it has been demonstrated that an abrupt change in cell energy metabolism accompanies the onset of mineral formation. Specifically, it has been found that pre-calcific, dividing cells exist in a high energy, reduced state. Also, changes in the content of intracellular phosphorus pools may be directly involved in supplying the initial inorganic phosphorus to the mineralizing matrix.

Changes in cell energy status may also play a role in the movement of calcium across cell membranes.

Enamel contains a complex mixture of proteins which appear to play a central role in the production and development of enamel. The determination of the number of these proteins, their structures and sequence of appearance and disappearance during enamel formation is essential to an understanding of this process. It is not known whether each of the components of the mixture represents a single protein, the product of an individual gene, or whether the components are interrelated. In order to define these relationships, enamel proteins were extracted and partitioned into amelogenin and enamelin fractions and injected into mice for the preparation of monoclonal antibodies. Although several attempts were made to raise monoclonal antibodies to each protein fraction, monoclonal antibodies were obtained only against the amelogenin fraction. Use of these antibodies should lead to a better understanding of the spatial relationship of the proteins of developing enamel to the mineral component and of their function in development. Further attempts are being made to produce monoclonal antibodies to the enamelin group of proteins, and to determine the immunologic relationships among the proteins.

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987
Res. centers				
Number	5	5	5	5
Amount	$7,599,000	$7,272,000	$7,272,000	$6,367,000

National Institute of Dental Research

Intramural Research

Public Health Service Act, Title IV, Parts C and I

1987 Authorization: Indefinite.

Budget Authority:

1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987	Increase or decrease
$20,004,000	$19,135,000	$19,135,000 (FTEs: 255)	$20,303,000 (255)	+$1,168,000 (--)

Purpose and Method of Operation

The intramural research program is carried on in eight laboratories and branches. A dental clinic and a pain research unit are maintained in the NIH Clinical Center to provide service for certain patients in the NIH Clinical Center programs and for the purposes of conducting clinical research. The intramural program also includes a major new initiative of epidemiology, biometry, and disease prevention programs which plans, develops, directs, and applies epidemiological methodologies to investigation of oral diseases and disorders and conducts clinical, field, and related studies in the prevention of oral disease.

The research program encompasses basic and clinical research efforts directed toward improvements in the diagnosis, prevention, and treatment of caries, periodontal and oral soft tissue diseases, oral tumors, congential abnormalities and diseases, orofacial pain, and diabetes. Varied approaches are required in the study of these conditions. The investigative tools employed are those of biometrics, biochemistry, biology, biophysics, immunology, microbiology, neurophysiology, virology, behavioral science, and clinical dentistry.

Rationale for the Budget Request

The 1987 budget request for intramural research is $20,303,000.

Cell Culture Models of Normal and Diseased Bone

The bones and cartilaginous tissues of the skeleton are derived from cells that form and maintain the basic support structures of the body throughout life. These highly specialized cells produce the complex macromolecules found in extracellular matrices which confer unique biomechanical and metabolic properties to bones and joints. These matrices and the cells that maintain them are the targets of a myriad of regulatory hormone and growth factors that control skeletal growth and mineral metabolism and maintain the balance necessary for sound musculoskeletal health. Disturbances in the maintenance of skeletal tissue at the regulatory, cell or molecular level lead to major diseases in developing as well as in mature individuals. These diseases include the heritable "brittle bone" disease of children, osteogenesis imperfecta, acquired nutritional deficiences such as osteomalacia and rickets, and crippling diseases of the aging, such as osteoarthritis and osteoporosis.

NIDR intramural scientists have developed special cell culture techniques which allow studies of human bone-forming cells (osteoblasts) from donors of varying age and bone-wasting conditions. Similar cells from bovine bone have been used to construct cDNA libraries for the bone genome from which the genes for two important components of bone matrix, osteonectin and the bone proteoglycan, have now been cloned. Both of these proteins, along with several other skeletal and dental tissue proteins, were discovered by NIDR intramural scientists. These investigators have now initiated an extensive study of bone formation and metabolism. They are using the cDNA probes as well as monoclonal antibodies to these proteins, in studies of human bone cells obtained from osteoporotic patients and normal controls and from children suffering from osteogenesis imperfecta. Results should provide a sound base for cataloguing the complex regulatory mechanisms controlling healthy skeletal function throughout life.

Osteogenin: A New Bone Growth Factor

In other studies these investigators have isolated a protein in demineralized bone matrix powder that appears to be the factor responsible for the regeneration of bone in clinical conditions of bony defects. These studies will permit investigation of the origin and mechanism of action for this important bone inductive agent. Eventually, recombinant DNA procedures might be used to produce this factor for general use in reconstructive surgery.

Work continues also on cartilage organ culture models for studying degenerative joint diseases such as rheumatoid arthritis. Studies have shown that early metabolic changes can be fully reversed with proper maintenance of the cartilaginous tissue and removal of the degenerative agent. These organ cultures are important models for normal cartilage metabolism and provide hope that methods aimed at early detection of joint disease can prevent the sequence of events leading to irreversible cartilage changes and subsequent bone destruction.

Intracellular Molecular Signals

Cyclic adenosine monophosphate (cyclic AMP) is an important intracellular signaling molecule in many cells. It is generated enzymatically when certain hormones or neurotransmitters interact with cell surface receptors, and its principal intracellular function is to activate cyclic AMP-dependent protein kinase. This enzyme adds phosphate groups to certain proteins, which regulate their function. The activity of cyclic AMP-dependent protein kinase is a critical step in the events leading to secretion of proteins and enzymes by many salivary gland cells. Monoclonal antibodies to the regulatory subunit of cyclic-AMP dependent protein kinase from rat parotid gland have been prepared and are being used in subcellular localization studies. Using electron microscopic immunocytochemical techniques, the regulatory subunit has been localized to regions of dense chromatin in the nucleus and in cytoplasmic regions rich in endoplasmic reticulum membranes in several cell types. These localizations are consistent with the hypothesis that the enzyme regulates the transcription of nuclear genes as well as regulating certain steps of the secretory process. Recently, the regulatory subunit has been found in parotid secretory granules and is secreted into the saliva. Now it appears that the regulatory subunit is found in the secretory granules of other salivary glands and also in glands associated with the gastrointestinal and reproductive systems. The unexpected widespread occurrence of this protein in glandular secretions suggests that it has an important extracellular function in addition to its better known intracellular role. Current research efforts are examining the localization and synthesis of the regulatory subunits. These basic studies will provide fundamental information on secretory mechanisms with the potential of understanding and developing better treatments or means of prevention for secretion-associated disorders.

Saliva Secretion Studies

Saliva plays a critical role in the defense and maintenance of all oral tissues. Perturbed salivary gland function results in increased dental disease (caries, periodontal conditions), difficulties in eating (chewing, tasting, swallowing) and increased risk of systemic infection due to compromise of the mucosal barrier and colonization of the mouth by atypical, opportunistic microorganisms. Hypofunctional salivary glands are early and hallmark findings in several significant diseases such as cystic fibrosis and autoimmune disorders.

Salivary glands secrete water, salts and proteins in response to neurotransmitter stimuli. Several advances in understanding the cellular events leading to saliva secretion have been made. For example, the major transport system responsible for driving saliva formation (water and salt transport) has been identified and characterized. This system is a $Na^+/K^+/2Cl^-$ cotransporter located in the basolateral membrane of salivary acinar cells. This system is known to be used in transporting the radionuclide ${}^{99m}TcO_4^-$, the most commonly used radionuclide in medicine, into epithelial cells. Together, these findings have allowed for the first time a clear interpretation of the ${}^{99m}TcO_4^-$ scan used for the diagnosis of dysfunctional salivary glands, and have formed the basis for new and effective treatments for such conditions.

Progress also has been made in understanding the assembly and transport of acinar cell secretory proteins. Detailed studies have defined the mechanism by which activated neurotransmitter receptors coupled to cyclic AMP generation (e.g., beta-adrenoreceptors, VIP receptors) lead to altered secretory protein glycosylation and function. This process involves a phosphorylation: dephosphorylation of microsomal dolichol-linked glycosyltransferases. These findings are providing clues to understanding the basis for oral complications resulting from impaired salivary glands which are still capable of water and salt secretion.

Refinements in Diagnostics

The insidious nature of many dental disorders coupled with the fact that the most significant of these, dental caries and the periodontal diseases, can lead to irreversible degenerative changes, assures that the most effective strategies for clinical management are preventive or at least interceptive.

Several new diagnostic tests are being studied to determine optimum treatment alternatives for oral conditions. These efforts include fabrication and testing of new computerized dental x-ray equipment which can display isolated slices of oral tissues derived from conventional x-ray projections. This machine also will permit isolation of minute changes over time. The associated x-ray dose is anticipated to be lower than that produced by existing equipment. Another technique being explored is a small device which may be able to determine whether a tooth is dead or not by a simple analysis of the color of light scattered from a beam which has been directed toward the tooth.

Prevention and Treatment of Herpes Simplex Virus Infections

Herpes simplex virus (HSV) is a common cause of recurrent sores involving the skin, eyes, lips, or genital area of many patients. During the initial infection, the virus enters the nervous system and may remain there permanently in a latent form. Periodically, the virus may reactivate and travel to the skin surface to cause the characteristic herpes sore. Infrequently, a life-threatening infection may develop, such as herpes encephalitis (an infection of the brain), herpes neonatorum (infection of newly born children), or disseminated herpes simplex (in a patient whose immune system is impaired). Herpes keratitis (an eye infection) is also a leading cause of blindness in the U.S.

NIDR intramural investigators are exploring three approaches to control HSV infection. First, in collaboration with colleagues at the National Institute of Allergy and Infectious Diseases, a vaccine has been developed and tested which is aimed at protecting patients from initial infection. The vaccine was developed by inserting a gene for a herpes simplex virus protein into vaccinia virus, the virus used for vaccinating against smallpox. This recombinant vaccinia virus vaccine was used to immunize mice. In experiments reported in 1985, the vaccine protected mice against infection with both HSV$_1$ (the type of herpes that causes cold sores) and HSV$_2$ (the type of herpes that causes genital sores). Experiments now show that these vaccinated mice remain protected against infection with HSV after one year. This is the first study on the duration of protection afforded by a genetically engineered vaccine against HSV. Further studies are being done to examine the effect of booster doses of the vaccine. The possibility of testing the vaccine in human subjects is also being evaluated.

A second approach toward controlling infection with HSV is aimed at limiting the severity of infection once it is established. An antiviral drug, acyclovir, has been shown to be effective in reducing the symptoms of initial and recurrent infection with HSV. The drug has also been shown to reduce the frequency of reactivation when given prophylactically on a daily basis in patients with genital herpes. Current studies are evaluating the effect of acyclovir in blocking reactivations of HSV in patients with frequently recurring herpes labialis (cold sores).

A third approach toward controlling infection by HSV is aimed at identifying the factors that trigger a recurrence. Candidates for such triggers include fever, sunlight, physical trauma, the menstrual cycle, and emotional stress. Over the past year, NIDR investigators and colleagues from NIAID have developed a human model for studying reactivation of HSV and identifying factors that trigger reactivation. Patients with recurrent HSV on the buttocks were exposed to ultraviolet light, inducing a small sunburn in the area of HSV recurrences. Sixty to 70% of the time, these patients developed a recurrence within six days after such exposure. Thus ultraviolet light (a component of sunlight) and perhaps sunlight may be a trigger for reactivation of HSV. Further studies will determine if the use of sunblocking agents can prevent reactivation under natural conditions. In addition, this model makes it possible, for the first time, to study the early phases of reactivation prior to the onset of symptoms. The changes in skin produced by ultraviolet light also may provide a clue to the mechanism of reactivation triggered by other stimuli such as trauma. Finally, this model provides a system for directly testing the ability of a variety of drugs to block reactivation.

Virus-Induced Diabetes

One of the major forms of diabetes mellitus is insulin-dependent diabetes mellitus (IDDM), also known as type 1 or juvenile diabetes. IDDM is caused by the destruction of insulin-producing beta cells in the pancreas. This results in reduced production of insulin and increased levels of blood glucose. What destroys the beta cells in human patients is not clearly known.

Previous studies from NIDR showed that encephalomyocarditis (EMC) virus and the members of the Coxsackievirus B group can cause diabetes in mice by infecting and destroying beta cells. There are also several lines of evidence to suggest that Coxsackieviruses can cause occasional cases of IDDM in humans. Since the number of well-documented viral-associated cases in humans is small, NIDR investigators, in collaboration with colleagues at NIAID, have developed a non-human primate model of virus-induced diabetes. Patas monkeys, when infected with Coxsackievirus B_4 or treated first with a subdiabetogenic dose of streptozotocin (a beta cell toxin) and then infected with Coxsackieviruses B_4 and B_3, developed transient diabetes. This observation in monkeys adds support to the hypothesis that under certain circumstances viruses can cause abnormalities in glucose metabolism and produce diabetes.

Molecular Mimicry

Viruses may also be involved indirectly in the destruction of host tissues by a mechanism known as molecular mimicry. An antigenic determinant on the virus might be similar to an antigenic determinant on host cells. If this is so, then certain antibodies made against the viruses might also react with host cells (molecular mimicry). Investigators at NIDR have tested over 600 different monoclonal antibodies made against 11 different viruses for their reactivity against normal uninfected tissues. Surprisingly, a very high percentage (about 4.0%) of these antibodies reacted with human cells in various tissues, showing that molecular mimicry is a very common phenomenon. Thus antibodies raised during a viral infection might bind to and damage host cells. The possibility that molecular mimicry may play a role in a variety of autoimmune diseases such as IDDM, multiple sclerosis and lupus erythematosus is now under investigation.

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Functional Studies of Connective Tissue Matrices

The fundamental role of cartilage and of basement membrane in establishing the form of the whole organism and its specific tissue compartments is well recognized. These extracellular matrices are characterized by certain functionally important macromolecules. Rapid progress has been made in identifying these molecules and in establishing the processes by which they form the supramolecular complexes which make each type of matrix unique. Matrigel, a supramolecular complex prepared from basement membrane components, has been used to study the action of basement membrane matrix on cells in culture. Many epithelial cells in culture are activated to a more tissue-like form and assume in vivo functions not previously expressed in culture, when placed in contact with matrigel. For example, if small clusters of cells isolated from embryonic exocrine and endocrine glands are placed on matrigel, they will recombine into functioning organelles in culture. Nerve cells cultured on matrigel elaborate more neurites, and their accompanying Schwann cells elongate and produce myelin. The clinical possibility exists that peripheral nerve regeneration may be greatly improved if the severed nerve is placed in a matrigel-filled tube.

The regulation of connective tissue genes is under study using recombinant DNA technology. Certain portions of the gene serve as promoters and control the expression of the gene. The promoter regions for the gene coding for type II collagen (a cartilage protein) and for the laminin B1 chain (which codes for a basement membrane protein) have now been identified. Plasmids have also been constructed containing various parts of the promoter region of the type II collagen gene coupled with the bacterial gene chloramphenicol acetyltransferase. These constructs allow study of the regulation of these genes in transgenic mice and in cell cultures. Initial studies indicate that specific DNA segments of the promoter region of this gene appear to act either as negative or positive controlling elements for the expression of the type II collagen gene.

Major progress has been made during the last year in the isolation of cDNA and genomic clones encoding proteins specific for cartilage and for basement membranes. cDNA clones for two major cartilage-specific proteins, link protein and the proteoglycan core protein, have been isolated and characterized by DNA sequence analysis. The striking internal homology within the deduced link protein sequence suggests that the protein evolved by duplication of a primordial gene. Clones containing cDNA for the A, B1, and B2 chains of laminin have been isolated. The nucleotide sequence of the entire B1 chain of laminin has been determined. Computer analysis of the deduced amino acid sequence predicts that the B1 chain is comprised of at least four distinct structural domains. The most striking feature is that two domains contain a cysteine rich homologous stretch of about 50 amino acids which is repeated many times. The gene for the B1 chain has also been isolated. Approximately 65 KD of the gene contains at least 37 exons with an average size of 200 bp. The transcription initiation site was determined, and the promoter region of the gene was characterized by DNA sequence analysis. The unique feature of the promoter region of this gene is that there are no "TATA" and "CAT" box sequences such as are often found in the promoter region of eukaryotic genes. Using restriction enzyme fragment polymorphism, abnormalities of these genes are being examined in patients with inherited diseases. These studies depend on the rapid progress that is being made in the isolation and structural characterization of the genes responsible for matrix synthesis.

The Establishment and Colonization of Oral Pathogens

The initiation of chronic periodontitis is a consequence of bacterial colonization of oral tissues which results in the accumulation of dental plaque. Investigation of the molecular events involved in plaque formation, therefore, are of paramount importance in clarifying these disease processes. Certain oral bacteria possess surface structures that allow them to attach directly to oral tissues. Other oral microorganisms have evolved specialized surface structures that mediate attachment to other bacteria in a highly specific manner. A major emphasis of NIDR intramural research is the complete chemical characterization of these surface molecules (adhesins). This information will provide a rational approach for interventions directed toward preventing bacterial colonization of oral tissues and thus inhibiting induction and progression of periodontal diseases. Research strategies employed to identify and characterize the adhesin molecules involve immunochemical and biochemical techniques, genetic manipulation of the organisms, and the use of recombinant DNA technology. This work has led to the identification and isolation of surface adhesins from *Capnocytophaga* species that mediate attachment of these organisms to species of *Actinomyces* or *Streptococcus.* Similar cell surface adhesins have also been isolated from *Bacteroides* species. Molecular cloning techniques have been used to identify genes from *A. viscosus* encoding for protein subunits that permit attachments by the microbe to epithelial cells or other bacteria. This year a gene from *A. viscosus* has been identified that encodes for a subunit of the adhesin responsible for the organism's ability to attach to the tooth surface. Work is now under way to determine the protein structure of these adhesins by sequencing the respective genes. These adhesins may also participate in the destruction of oral bacteria by phagocytic cells. Thus, the interaction of one type of adhesin with carbohydrate receptors on polymorphonuclear leukocytes results in the ingestion and killing of these bacteria by the leukocytes.

The attachment of bacteria to oral tissues and to one another is an established prerequisite for the initiation of both periodontal diseases and dental caries. Another critical step in the infectious process is the subsequent ability of the microorganisms to colonize; that is, their ability to metabolize available nutrients and to proliferate. One consequence of the metabolic activities of some members of the oral flora is the elaboration of products that are destructive to the oral tissues. For example, the lactic acid bacteria produce organic acids that are responsible for the dissolution of tooth enamel, while other members of this complex flora produce various species of oxygen radicals and extracellular proteases that are toxic to oral tissue. Studies of microbial metabolism, therefore, are undertaken to provide insight into means for developing methods for the control or manipulation of the oral flora and their cytotoxic products at the biochemical level. The complex enzyme system responsible for the transport of dietary carbohydrates across the cell membranes of oral lactic acid bacteria represents one current area of investigation. This initial step in the metabolism of sugars was selected for study because most bacterial transport systems are quite different from those found in eucaryotic cells and thus may represent a unique site for the specific inhibition of microbial growth. Results from this study have shown that various sugar analogues, as well as the widely used sugar substitute, xylitol, are potent growth inhibitors for various oral lactic acid bacteria. These compounds have been shown to act in a very unusual manner. They are actively transported into the bacterial cell by the sugar transport enzyme system although they cannot be metabolized. Instead, they are rapidly dephosphorylated intracellularly by another enzyme and exported from the cell. Repetition of this process constitutes a futile cycle that depletes the cell of energy and inhibits growth. The discovery of these novel futile cycles may point the way to new strategies for the development of antimicrobial agents.

Current Immunological Studies of Acute and Chronic Inflammation

A major effort in NIDR intramural research is to understand the mechanisms involved in the release of inflammatory mediators from basophils and mast cells. Such mediators play important roles at sites of acute inflammation and in immediate hypersensitivity reactions. The primary initiating event depends on the antibodies which are attached to specific receptors on the cell surface. The experimental approach has been to study the molecular sites on the immunoglobulin critical for its binding to the receptor and obtain a better definition of the receptor molecule on the cell surface. The research has utilized the monoclonal hybridoma technique to define the cell surface molecules that are involved in the stimulation of these basophils or mast cells. Reagents have been prepared that recognize the immunoglobulin receptor on these cells. This is the critical point at which immunological injury results in the release of inflammatory mediators (histamine, prostaglandins and leukotrienes). Some of these hybridoma reagents have also defined molecules on the cell surface that are capable of turning off this response. Using these hybridoma reagents, the surface molecules are being purified so that their structure can be defined and the early steps in cell activation understood. This understanding can lead to better methods for preventing the release of mediators of inflammatory reactions. It is also critical to pinpoint the sites on the immunoglobulin molecule which react with receptors on the cell surface. Using hybridoma technology, a number of reagents have been prepared that define sites on the immunoglobulin molecule that are involved in interactions with the receptor. This knowledge might lead to the design of better drugs that could interfere with the interaction of immunoglobulin and its receptor and thus prevent unwanted inflammatory reactions.

Another major area of research is focused on understanding the biochemical mechanisms involved in the release of inflammatory mediators. Cultured basophil cell lines have been developed and are proving to be very useful. Large numbers of cells can be easily cultured for the measurement of the biochemical changes when the cells are activated. A number of important biochemical steps have now been described, including the activation of enzymes which secrete arachidonic acid, a precursor for inflammatory mediators such as the prostaglandins and leukotrienes. Other critical events are the changes in the level of calcium inside the cell and changes in cellular proteins. Mutants of these cultured cell lines have also been selected which cannot release inflammatory mediators. These cells are then used to study biochemical pathways involved in the secretory process. These studies should lead to a better understanding of secretory events in cells with the possibility that more effective means can be designed to diminish inflammatory reactions.

In an experimental animal model NIDR investigators are also exploring the mechanisms whereby certain acute inflammatory lesions progress to chronic destructive lesions. Following the injection of group A streptococcal cell wall (SCW) antigens into genetically susceptible rats, the antigen is dispersed primarily to the spleen, liver and peripheral joints where it initiates an acute inflammatory response. Subsequently, the affected animals develop chronic inflammation leading to proliferative and erosive polyarthritis in the joints and granulomatous lesions in the liver. Both lesions require local deposition and persistence of the antigen and exhibit dramatic effects on the surrounding connective tissue. The development of these bacterial-induced lesions is dependent upon genetic susceptibility and hormonal factors. Of significant interest is the apparent dissociation between the cellular and biochemical events associated with the acute and chronic lesions. Investigations in this model currently focus on the mechanisms of progression from acute to chronic inflammatory disease and their potential relevance to delineating similar mechanisms which may occur in the conversion of acute gingivitis into chronic periodontitis. The initial event following deposition of SCW in the tissues is an acute inflammatory response including exudation of neutrophils, mast cells and mononuclear cells with the release of mediators of immediate hypersensitivity. This acute response peaks three days after injection of the bacterial cell walls and then subsides. The subsequent histogenesis of the lesions involves the infiltration of circulating mononuclear cells, aggregation and maturation of these cells, and the recruitment and proliferation of fibroblasts which are instrumental in the degradation of connective tissue (arthritis) and in the development of fibrosis (granuloma). Although the evolution of this series of events is immunologically specific and is dependent upon T cell function and the mechanisms associated with cell-mediated immune reactions, the acute and chronic phases of the lesion appear to be mechanistically distinct. In the absence of functional T lymphocytes as occurs in athymic (nude) rats, the injection of SCW induces only acute lesions in the liver and in the joints demonstrating that the T cells are critical to the evolution of the chronic, but not the acute disease. Furthermore, pharmacologic inhibition of T cell function by the immunosuppressive drug cyclosporin A similarly inhibits the development of erosive arthritis and granuloma formation, but has no effect on the transient acute inflammatory lesions. These observations demonstrate differences in the cellular requirements for the acute inflammatory response and for the chronic destructive lesions. Further characterization of the cellular and molecular mechanisms responsible for these distinct phases of the inflammatory process and the regulatory role of cell-derived inflammatory mediators will provide insight into potential mechanisms of therapeutic intervention.

Progress in Pain Control

Basic research studies have continued to advance knowledge of neural pathways and chemicals involved in pain transmission. A new pathway carrying information about tissue-damaging or noxious stimuli to the midbrain has been discovered. This pathway may be involved in the motivational and autonomic nervous system consequences of noxious stimulation. Other studies have demonstrated an interaction between serotonin-containing cells and norepinephrine-containing nerve terminals in the medulla. These chemicals play an important role in the modulation of sensory messages related to pain. This modulation appears to occur at these brain stem levels as well as in the spinal dorsal horn. Some serotonin-containing cells in the brain stem send their axons to the spinal cord. Substance P, a neuropeptide, is found to co-exist with serotonin in some of the cells whose axons terminate in the dorsal and ventral horns of the spinal cord. Morphine, which mimics the action of naturally occurring opioid peptides in the brain, has a direct effect on medullary dorsal horn nerve cells and alters the perceived intensity of noxious stimuli. Increased knowledge of the neurochemistry of pain will ultimately lead to the development of new and improved modalities for treating pain.

Recent advances in the treatment of painful conditions resulting from nerve damage have been made in the NIH Ambulatory Care Research Facility. Tricyclic antidepressant drugs are effective in the treatment of painful diabetic neuropathies. This effect is dose-dependent and independent of the effect of the drug on depression. Other studies suggest that these drugs are also effective in the treatment of post-shingles pain and atypical facial pain. New studies are under way in the treatment of muscle tension headache. The previous finding that the brain's own pain-suppressing compounds are released during stressful procedures is being used to develop new methods for activating or enhancing the activity of these systems.

Epidemiology and Oral Disease Prevention Program

The purpose of this activity is to expand and improve information on the epidemiology and prevention of oral diseases. The activity involves direct operations research, both laboratory and clinical, and research and development contracts.

The most dramatic epidemiologic finding in dentistry in recent years came from a nationwide survey completed by the NIDR in 1980, which demonstrated a major decline in dental caries among U.S. school children. Whether this trend is continuing is a question of highest priority to oral health, and will be addressed by a repeat national study of the oral health status of children, scheduled to begin in Fall, 1987. Meanwhile, collaboration continues with several European investigators to collect standardized data on trends in oral diseases in other populations, with and without caries-preventive activities comparable to those in the U.S.

Much less is known about the prevalence, distribution and correlates of periodontal diseases. In January, 1987, the Institute will conclude an extensive National Survey of these conditions, as well as root surface caries, among adults and the aged. In addition, more extensive studies are planned of incipient signs of periodontal disease in adolescents, to determine whether children at high risk of destructive periodontitis can be identified by mid-teen years. A multicenter collaborative study has just begun in an effort to find differences in microbiologic, immunologic or biochemical parameters among older adults with and without a history of periodontal disease.

Very little clinical research on oral cancer or precancerous lesions has been conducted in the U.S. in recent years. During FY 1987, pilot studies will begin on selected populations, especially those believed to be at high risk because of habits such as extensive use of smokeless tobacco.

During the year, data collection will be completed and analyses begun in a longitudinal study of the relationship between caries incidence and dietary sources will also be analyzed.

Successful development continues of a controlled-release system for low-cost administration of topical fluoride and other preventive agents. A six-month clinical trial in children has been completed, and more extensive study of this system is planned for 1987. Research will include an investigation of the effectiveness of the slow-release system in preventing caries in high-risk cancer patients who suffer xerostomia secondary to therapeutic irradiation of the head and neck.

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National Institute of Dental Research

Research Management and Support

Public Health Service Act, Title IV, Parts C and I

1987 Authorization: Indefinite.

Budget Authority:

1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987	Increase or decrease
$6,870,000	$6,508,000	$6,508.000 (FTEs: 74)	$6,741,000 (74)	+$233,000 (--)

Purpose and Method of Operation

This activity provides the leadership and management direction of the entire Institute in addition to the administrative management and scientific direction in the review, award and monitoring of research grants, training awards, and research and development contracts. Associated with this activity is the immediate Office of the Director and the Institute's scientific and administrative staff.

This activity will continue to provide the leadership, program guidance, and overall administration for the programs and information directed to scientists, dental practitioners, and the public, in addition to continuing to administer, manage, and review the Institute's grant and contract programs.

Rationale for the Budget Request

The 1987 request for research management and support is $6,741,000, an increase of 233,000 over the 1986 level of $6,508,000.

During 1987 some specific major activities will include:

o Initiation of World Health Organization International Collaborative Study of Oral Health outcomes - contract funds for U.S. portion and for portion of overhead costs in Geneva.

o Updating of the NIDR Long-Range Research Plan FY 1985-89, Challenges for the Eighties leading to development of Long-Range Research Plans for 1990-1994.

o Development of an oral health promotion research program activity involving demonstration research projects at worksites and at other community settings. The focus will be on prevention of oral diseases among adults and family units.

National Institute of Dental Research

Detail of Permanent Positions

	1985 Actual	1986 Estimate	1987 Estimate
ES-4............................	7	7	7
GS/GM-15.........................	18	18	18
GS/GM-14.........................	18	19	19
GS/GM-13.........................	15	14	14
GS-12............................	15	15	15
GS-11............................	25	24	24
GS-09............................	24	25	25
GS-08............................	7	8	8
GS-07............................	27	27	27
GS-06............................	19	20	20
GS-05............................	20	19	19
GS-04............................	8	8	8
GS-03............................	4	4	4
GS-02............................	2	2	2
Subtotal......................	209	210	210
Grades established by Act Of July 1, 1944 (42 U.S.C. 207):			
Director Grade...............	21	22	22
Senior Grade.................	5	5	5
Full Grade...................	2	2	2
Subtotal...................	28	29	29
Ungraded.........................	48	46	46
Total permanant positions........	285	285	285

WEDNESDAY, MARCH 12, 1986.

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

WITNESSES

DR. MURRAY GOLDSTEIN, DIRECTOR, NINCDS

DR. JAMES B. WYNGAARDEN, DIRECTOR, NIH

DR. THOMAS MALONE, DEPUTY DIRECTOR, NIH

RICHARD SHERBERT, EXECUTIVE DIRECTOR, NINCDS

WILLIAM MATTHEWS, BUDGET OFFICER, NINCDS

DENNIS P. WILLIAMS, ACTING DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. NATCHER. At this time we take up the budget request of the National Institute of Neurological and Communicative Disorders and Stroke.

We have before the Committee Dr. Murray Goldstein, the Director.

Dr. Goldstein, it is a pleasure to have you back before this Committee. You have been here before.

Dr. GOLDSTEIN. A few times.

Mr. NATCHER. Yes, sir.

And we are glad to have you. And before you start in, Doctor, tell us who you have with you there at the table.

Dr. GOLDSTEIN. Thank you very much, Mr. Chairman.

May I introduce on the far left the Executive Officer of our Institute, Mr. Richard Sherbert. On my immediate left, the Institute's Budget Officer, Mr. William Matthews.

Mr. NATCHER. We are delighted to have all of you with us at this time. And, Doctor, we will be pleased to hear from you.

Dr. GOLDSTEIN. Thank you, Mr. Chairman.

I have submitted my opening statement to the Committee but, with your permission, I would like to touch on a few highlights that I think would be of value and interest to the Committee.

SENATOR JACOB JAVITS AWARDS

Before I begin though, sir, if I may, I would like to comment about our very special program which honors a previous Member of the House, Senator Jacob Javits.

The Senator was previously, as you know better than I, a Member of the House. He was very, very interested in health research. During the last few years, because of his own illness, he paid particular attention to the research problems of the brain and nervous system.

We were able to establish, with this Committee's assistance, two very specific programs which honor his accomplishments. The first is a Program of Neuroscience Investigator Awards, which gives the brightest and the best of our investigators seven years of research support to explore the unknown. Also we have initiated a small program of Senator Jacob Javits' Neuroscience Centers of Excellence, of which there are four now operational.

My final comment on that, sir, is I believe these are living memorials to a superb member of our legislature and we would hope to continue this memorial in his name.

I would like to report on three specific scientific activities in which I believe this Committee would be most interested.

EC/IC CLINICAL TRIAL

The first is the completion of a clinical trial which I had mentioned in the past. About 20 years ago, with the best of logic, a group of neurological surgeons were able to develop a most unusual technique by which they were able to bypass an obstruction in the blood flow to the brain. In other words, when a blood vessel of the brain became obstructed, they developed a relatively simple operation in which a blood vessel from the scalp was introduced into the brain past the obstruction and were able to revascularize the brain. This was offered as a potential treatment for stroke; an EC/IC anastamosis. It clearly was a very thoughtful and promising procedure.

It has become one of the most common of all neurosurgical procedures. However, in the interest of science and the public health, we thought that we ought to evaluate this procedure by means of a clinical trial and find out how effective it is in preventing and treating stroke.

This last year—actually just a few months ago—we were able to report on the results of that clinical trial. I am very sorry to say, sir, it is not useful for the prevention or treatment of stroke. It is of no benefit to the American public in the treatment of this disease.

I am bringing these results to your attention for two reasons. The first is that with the publication of the results of the study, we will now save the American public about $40 to $50 million each and every year. The study cost $9 million over a nine-year period.

The second is that we are also helping or protecting the health of the public. This procedure will not be used any longer because of its morbidity and lack of effectiveness. And so we have completed a study which is a landmark in the NINCDS' activity.

RESTITUTION OF FUNCTION

The second item I would like to bring to your attention is an area of research which is most exciting; we call it restitution of function.

As we know so well, we are born with all the brain cells we are probably ever going to have, something in the order of magnitude of 10 billion nerve cells in the brain.

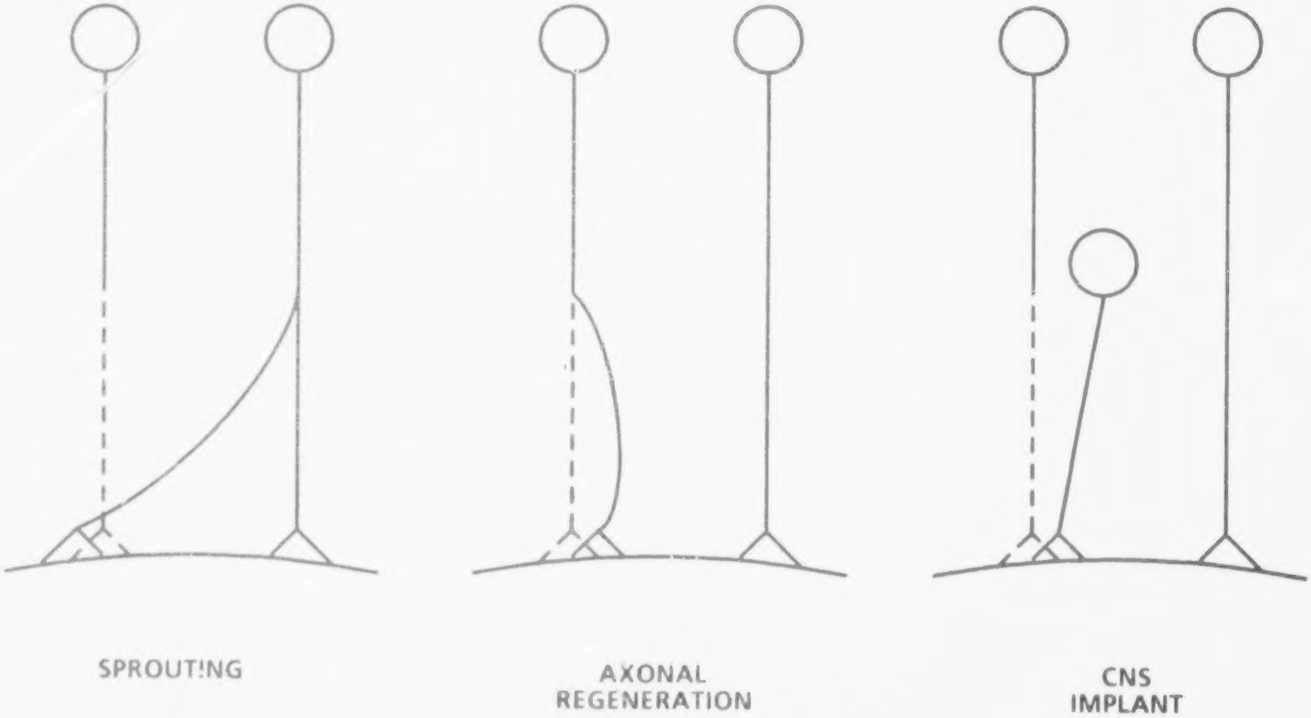
I was taught as a young man, as were my colleagues, that once a brain cell was damaged, it was so highly specialized in function that it could not repair itself. It generally died after injury such as stroke or head injury, or a number of other disorders.

Fifteen years ago, if I were before this Committee, I would have made that statement as absolute truth. The fact of the matter is we were wrong. The brain can repair itself. And it does so in three different ways.

With your permission, I would like to point them out, sir.

[The following was provided for the record:]

RESTITUTION OF FUNCTION IN BRAIN & SPINAL CORD


SPROUTING
AXONAL REGENERATION
CNS IMPLANT

Dr. GOLDSTEIN. The first of these is a process that goes on in a damaged brain in response to injury, a process we call sprouting. This is a process, a methodology by which when one nerve cell is damaged, the nerve cell next to it sends out a sprout, a twig, which grows to the target that has lost its nerve. This is an ongoing process that goes on in the human brain regularly. It is the reason why, if a person has a stroke, seven, eight, nine months later, we recognize the person has had some return of function. The arm that was paralyzed is now moving a bit. The speech that was gone has now partially returned.

We thought it was all due to rehabilitation, and I am not in any way denigrating rehabilitation as such. We believed it was due to teaching somebody how to use what he had left in a better way. We now know that is not the only reason, but that this process of sprouting is basic to the return of function.

What we are working on very diligently is how we can influence this process to increase its amount and speed.

The second process is perhaps one of the most exciting, and it could have a great impact on paraplegia. Once a brain or spinal nerve cell has been damaged severely and the long filament that goes from the brain down the back, say, to the big toe, once that has been damaged, we have always believed it would be impossible for the filament to regrow. Sir, we are regrowing these nerves right now in higher animals. Those nerve cell filaments are being regrown in spinal or head-injured animals.

Within several, perhaps three years, I am quite certain this will become an established and available methodology. But we have another problem. And that is how will this growing filament know where to go? It has got a long distance to go. And quite obviously if it is supposed to go to the big toe and goes to the bladder, we have not done very much for the patient. Therefore, we have got to learn how to control the growth. But that nerve cell knew where to go in the first place, when we were born. There was a code somewhere which told it where to go. Is the code still there? Can we reactivate it? Do we have to influence the growth artificially? We do not know the answer to that yet. I would hope in subsequent hearings I will be able to tell you more about it.

And the third process, sir, is crystal ball gazing. It is an aspiration; we call it central nervous system implantation.

I opened my statement by saying that we were born with about 10 billion brain cells, and that is all that we will ever have. Well, I am not sure of that.

Are we able to take nerve cells and put them into a person's brain and have them grow and begin functioning? I can tell you, sir, we can do it in a chimpanzee now. We can take nerve cells and put them in a damaged area of the brain. Those nerve cells became established, they release neurotransmitters and they alleviate the chimpanzee's neurological symptoms. We have not yet done this in humans. It will still be quite a while before we are ready to consider human research. This research is called central nervous system implantation.

I do not use the word "transplant" because we are not transplanting a brain from one organism to another. What we are doing is taking some few cells of a very specific nature and putting them in the brain. Obviously, this could be important in head injury, stroke and clearly Parkinson's disease. This latter is the model we are using. Perhaps in the future it may be useful in Alzheimer's disease. However, I do not know about that yet.

But this methodology now being developed, and I would hope in the reasonable future that I can tell you about progress to reinnervate the damaged brain. Implantation is another example of what we are calling restitution of function.

AIDS DEMENTIA

The final exciting area I would like to describe in neuroscience research is part of a discussion which I am sure you will hear more of when Dr. Fauci, my colleague who is Director of the Allergy & Infectious Diseases Institute, discusses AIDS.

But one new element of AIDS is a profound puzzlement. We now have distinct evidence of young people entering the hospital whose only presenting symptom is dementia—they are demented. It turns out that they have AIDS. We now have evidence that the AIDS virus can enter selected areas of the brain and nervous system, a system which is partially protected or isolated from the immune system. This is a profound problem because it is possible that the AIDS virus will take up housekeeping in the brain, be there for a period of time undetected by the body, and then suddenly become active, destroying brain tissue and producing dementia and other neurological symptoms.

Of equal concern is we now know of patients who had dementia, were sero-negative on blood testing, and on death clearly had the AIDS infection in their brain. When this virus enters the brain, it is an immunologically privileged environment which we have not considered previously. This raises new questions and new problems about AIDS infection that we have not considered adequately to date.

I am pleased to report that research grant money has been awarded by the NINCDS to investigators exploring this new area of AIDS as well as to scientists in our own laboratories. I hope to be able to describe progress more adequately next year.

In conclusion, sir, our budget request for 1987 is $399.351 million, and I would hope to be able to answer any of your questions.

Thank you.

[Statement follows:]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institute of Health

Statement of the Director
National Institute of Neurological and Communicative Disorders and Stroke

During the past thirty years, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) has focused its attention on the support and conduct of intensive research on the basic neurosciences and communicative sciences to serve as the basis for clinical advances. As a result and with the development of a broad core of understanding about the organization and pathology of the brain and nervous system, we are now prepared to reap the benefits of this focused activity; we are organizing the required research teams to intervene in some of the more than 650 neurological and communicative disorders that devastate the lives of millions of Americans and their families. These varied diseases affect all parts of the brain, the central and peripheral nervous systems, muscles and soft tissue, as well as being a central factor in dysfunction of the immune and endocrine systems. Some of the diseases under our purview, such as stroke kill their victims, adults or children, outright while others, such as, Batten's, Huntington's, Tay Sach's and Alzheimer's disease result in a lingering slow life-in-death with victims robbed of their mental and physical powers. Still others, such as amyotrophic lateral sclerosis (ALS), destroy the body's mobility, leave the brain intact, but eventually kill its victims. As Senator Jacob Javits has put it so vividly: "The living dead." Autism, hearing problems, aphasia, attention disabilities and epilepsy wreak havoc on the mind and our ability to function in society. Many neurological disorders are inherited or have a genetic component. Neurofibromatosis, tuberous sclerosis, Joseph's disease, Huntington's disease, Gaucher's disease and the other lipid storage diseases are passed on from parents to children. Some neurological disorders are even more mysterious. Tourette syndrome, with its uncontrollable outbursts, currently intractable forms of epilepsy, severe Parkinson's disease, myasthenia gravis, multiple sclerosis with all of its variations destroy the patient's life and add unmeasurable stress to families. Not only is the disability associated with these diseases destructive, but also the unpredictability of an attack or exacerbation further confounds the very act of living. We must remember that the impact of these diseases do not generally diminish over time. They are chronic; patients get worse. To date we have had few effective and safe therapies. The maladies are mysterious, complicated, and so far most have been resistant to the concerted efforts of our best minds.

But this is now changing. We are learning how to help and in some diseases to discard commonly used therapies which are of no value. In a few cases we can stem the tide of the illness.

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In other cases, we can control the symptoms and slow the still inexorable path of the disease. Further, research is clarifying current medical and surgical practices. For example, this year in a major international clinical trial, scientists supported by NINCDS discovered that a widely used neurosurgical procedure to direct blood past obstructed brain arteries is no more effective--and much less safe--than available medical therapy for preventing stroke. We now know that this commonly done surgical procedure, the extracranial/intracranial (EC/IC) bypass operation, should be abandoned as a therapy for stroke. The potential savings are immense, as an EC/IC operation costs an average of $15,000 and several thousand are performed in the United States each year. We are now preparing to evaluate the effectiveness of one of the most commonly performed surgical procedures in the U.S., carotid endarterectomy for the prevention of stroke. In addition, new pharmacologic methods are being developed and evaluated for protecting the threatened brain cell during the acute stroke period.

New epilepsy treatments are also emerging. Just as we discover serious and unwanted side effects with barbiturates, long an important part of antiepilepsy drug therapy, new surgical techniques are beginning to help those epilepsy patients whose seizures have not been controlled by drugs. Scientists are exploring such new experimental diagnostic techniques as magnetoencephalography (MEG), a sophisticated recording of the magnetic fields generated by the brain, to pinpoint the exact brain abnormality. With modern imaging techniques physicians are able to perform microsurgery and excise even the tiniest lesion responsible for the abnormal discharges of epilepsy.

Biotechnology advances are starting to make inroads in primary brain tumors, such as the gliablastomas, long recognized as among the deadliest of cancers. Little progress has been made in treating many primary brain tumors by conventional pharmacologic, radiation or surgical means; most of these tumors are difficult to treat and the prognosis is often poor. We are applying the technology of monoclonal antibodies and other emerging tools of the biotechnology revolution to improve the targeting of chemotherapy to the tumor. We are very excited right now by an NINCDS intramural project using fresh tumor cells treated with Interleuken-II to attack deadly glial brain tumors. These cells, produced from the live tumor cells of the individual patient, theoretically can attack each part of the highly diversified tumors and, thus, may be better able to destroy the tumor. The preliminary results are very promising. At therapeutic doses the treatment appears to be safe and nontoxic to the patient, a rarity in cancer treatments. Neuroscientists' efforts to understand and control Acquired Immune Deficiency Syndrome (AIDS) have also increased in the past year. To cite one example, scientists have discovered that AIDS is sequestered and replicates in the cells of the brain, perhaps even when it is quiescent in other parts of the body. Because the blood-brain barrier prevents most drugs from entering the brain, AIDS researchers now must not only find effective therapies for this deadly disease, but in cooperation with brain scientists must also devise a way to deliver it to the site of infection, the too-well protected brain.

The brain and the central nervous system are simultaneously sturdy and vulnerable. Once injured, once function is lost, restitution of function is difficult and could be impossible. Serious spinal cord injury and resulting paralyses have long been viewed as permanent. While at the moment we must still accept such injuries as immutable, we are beginning to develop the information necessary to challenge these theories. First, we are working to prevent the initial insult in a host of conditions including stroke, Parkinson's disease, and hearing disorders, as well as in spinal cord and head injury. Second, we are learning how to reverse these injuries and their effects and to restore function to a damaged nervous system; however, we cannot do it yet. The knowledge base is growing which may someday make available effective treatment of those diseases that now destroy parts of the brain and the central nervous system.

For example, in a recently completed controlled pilot study of Copolymer I in exacerbating-remitting multiple sclerosis, a frequent form of the disease, there was a significant reduction in the frequency of MS relapses in the Copolymer I group over the control group in the two years of the study. At the end of the trial, the patients treated with Copolymer I are significantly less disabled than their counterparts in the control group. Each MS attack causes additional scarring and loss of function of the central nervous system; the patient recovers less completely from each exacerbation. If we can decrease the number of attacks, we may halt the relentless loss of function associated with MS. We hope to learn more in a full-scale clinical trial of Copolymer I.

Another way to restore lost function is with a neuralprosthesis. The first but relatively crude cochlear implants are already available to help the profoundly deaf, but the future holds much more promise. While existing implants allow the wearer to identify the existance of sound and some of its coarse characteristics, multi-channel models now being designed may permit the profoundly deaf patient to discriminate between a telephone ring and a doorbell chime. Eventually, using computer assisted speech processors, the deaf should be able to interpret the electrical impulses of the human voice as actual, intelligible speech.

In past decades stroke treatment has seen little change; physicians have been powerless to stop the brain damage once the stroke begins. The findings of basic research are changing that unsatisfactory situation. For example, stroke patients used to be given intravenous solution containing glucose as soon as they were admitted to the hospital. Now we realize that glucose "overfeeds" the brain and actually acts to further threaten damaged brain cells. Stroke is now being treated with an entire armamentarium of modern medicine to keep brain cells alive until the acute stage of the stroke is arrested and the brain can make use of its amazing powers of survival. Scientists have discovered that brain cells deprived of oxygen and necessary fluids do not die immediately but can be maintained and regain function many hours after the initial injury. These exciting findings are preliminary, but point the way to further stroke and trauma research and demonstrate the ties and strong relationship between basic and clinical research.

Head and spinal cord injury destroy the lives of thousands of young Americans each year. Currently, only supportive and rehabilitative care is available; as yet effective methods are not available to treat paralysis or the seriously damaged spinal cord. In the past few years things have begun to change. Scientists using modern plastics and the techniques of bioengineering are learning how to allow a damaged nerve cell to grow again and even to grow within appropriate neuron bridges to their appropriate targets. While this work is still in its infancy, it is very promising and offers hope that indeed some day the paralyzed may walk again.

The implications are enormous. We anticipate these early results of basic science as they are eventually applied to the damaged nervous system will improve the quality of life of trauma patients as well as for patients with Alzheimer's disease, Parkinson's disease, or ALS. Thus, in addition to prevention as a primary goal of NINCDS research, restitution of function has also been designated as a primary target.

The ties between basic and clinical sciences, between science and medicine grow stronger and are our major modus operandi. Our commitment to basic research remains unwavering. An example of this commitment is our Javits program, mandated by the Congress. The NINCDS now supports 147 Javits scholars, each of whom is investigating a key, yet unsolved issue, in the neurosciences or communicative sciences. Demonstrating the importance of multi-disciplinary, comprehensive research centers are the four NINCDS Javits Centers of Neurosciences Excellence.

The NINCDS research program has reached its second milestone. The first was developing and establishing a cadre of basic and clinical scientists superbly trained in the "new" biology. The second milestone was the reevaluation of the understanding of the brain, the nervous system and human communication and recognizing its unique molecular and neurochemical properties. With a new core of understanding about the neurological and communicative system, the NINCDS is prepared to address the third issue of Institute responsibility--the prevention of neurological and communicative disease and the restitution of function where damage has been done by disease, trauma or genetic dysfunction.

Our budget request for FY 1987 is $399,351,000. I am pleased to answer any questions you might have.

Murray Goldstein, D.O., M.P.H.
Director, National Institute of Neurological and Communicative Disorders and Stroke

October 13, 1925, New York, New York

EDUCATION: B.A., New York University, 1947; D.O., Des Moines Still College of Osteopathic Medicine, 1950; M.P.H., University of California, School of Public Health, 1959.

PROFESSIONAL HISTORY: Director, NINCDS, 1982-present; Acting Director, NINCDS, 1981-1982; Deputy Director, NINCDS, 1978-1981; Medical Officer, Commissioned Corps, PHS (Assistant Surgeon General), 1953-present; Director, Stroke and Trauma Program, NINCDS, 1976-1978; Director, Extramural Programs, NINCDS, 1961-1976; Visiting Scientist, Mayo Clinic and Graduate School, Rochester, Minnesota, 1967-1968; Chief, Special Projects Branch, NINCDS, 1960-1961; Assistant Chief, Research Grants Review Branch, DRG, 1959-1960; Acting Chief, Section on Virus Diseases of the CNS, Bureau of Acute Communicable Disease, California State Department of Public Health, 1958; Director, Epidemiology and Biometry Training Grant Program, DRG, 1956-1958; Assistant Chief, Grants and Training Branch, NHI, 1953-1958.

PROFESSIONAL ORGANIZATIONS: American Academy of Neurology; American Association for the Advancement of Science; American Heart Association, Council on Stroke; American Neurological Association; American Osteopathic Association; Association for Research in Nervous and Mental Disease; Member, Board of Directors, John P. Robarts Research Institute, London, Ontario, Canada; Society for Neuroscience; The American Parkinson Disease Association, Medical Advisory Board; Eisenhower Institute for Stroke Research; United Cerebral Palsy Research & Educational Foundation, Board of Directors; Consultant (Neurology), Pan American Health Organization; Consultant, World Health Organization Program on Neurosciences; World Federation of Neurology; International Brain Research Organization; Commission on Alternative Health Care, U.S. Olympic Council on Sports Medicine.

HONORS, AWARDS: Beta Alpha Epsilon, Biology National Honor Society, NYU; Psi Chi, Psychology National Honor Society, NYU; Sigmi Alpha, Osteopathic Scholarship National Honor Society, College of Osteopathic Medicine; Delta Omega, Public Health National Honor Society, University of California; Doctor of Science (Hon), Kirksville College of Osteopathic Medicine; Doctor of Laws (Hon), New York Institute of Technology; Doctor of Science (Hon), University of New England; Doctoris Honoris Causa, Medical University of Pecs, Hungary; Certificate of Merit, American Neurological Association; 2nd Vice President, American Neurological Association; Silver Star, Purple Heart, U.S. Army; Meritorious Service Medal, Public Health Service; Distinguished Service Medal, U.S. Public Health Service; Founders Day Medal (S.S. Still Medal), University of Osteopathic Medicine and Health Sciences, Des Moines, Iowa.

RESEARCH OPPORTUNITIES

Mr. NATCHER. Thank you, Dr. Goldstein.

Now, your statement to the Committee speaks of more than 650 neurological and communicative disorders and states that you are organizing the required research teams to intervene in some of them.

Which disorders, Doctor, do you think are ripe for this sort of intervention at this time?

Dr. GOLDSTEIN. There are several vascular diseases of the brain that we commonly call stroke. Quite clearly, head and spinal cord injury, trauma to the brain and nervous system also must be included.

The third is a group of disorders that we call the neurogenetic disorders. These include a number of rare and not so rare diseases, neurofibromatosis, tuberous sclerosis, Huntington's disease. An area which is just really beginning to move ahead should be included and that is the communicative disorders, the disorders of hearing, language and speech.

I would identify these four areas as areas of the highest probability of important success now that we have trained an appropriate pool of investigators.

Mr. NATCHER. Doctor, how do you plan to go about organizing research teams for this purpose?

Dr. GOLDSTEIN. The best mechanism we have for research team work is what we call our Program-Project and Clinical Research Center mechanisms.

These mechanisms provide a team of investigators with the opportunity to work together towards a common goal, each investigator independent and of senior status. It is these two available mechanisms that provide us with the opportunities to accomplish that purpose.

CLINICAL RESEARCH

Mr. NATCHER. What kind of intervention generally do you speak of, Doctor?

Dr. GOLDSTEIN. By intervention I mean intervention at two separate levels, sir.

In the chronic diseases which are characteristic of the nervous system, there are a series of steps in the pathology of disease. We must first ascertain specifically where in the process of cellular destruction and degeneration is the most vulnerable point at which we can intervene, rather than randomly seeking possibilities.

The second is to be able to identify the specific therapeutic intervention, whether it be drug, surgery, or perhaps in this day and age genetic engineering by means of which we can intervene into the cycle of disease and disrupt it. In drug therapy, we call this the intelligent pharmacology in which we know what we are looking for and develop a specific drug, or it can be surgical procedure, to accomplish our therapeutic objective.

RESEARCH EMPHASIS

Mr. NATCHER. Do you intend to move from basic research to more applied research, such as clinical trials of promising drugs, Doctor?

Dr. GOLDSTEIN. May I say no, sir. What we plan to do is both. We still have so much to learn about the basic mechanisms of how the brain works and does not work that we are not prepared to abandon or deemphasize basic research.

The core of our activity will continue to be basic research. However, as opportunity and resources permit, we are now finally prepared to support some interventions; that is, increase our applied and clinical research. We would hope to be able to move forward with selected clinical intervention research programs in addition to our basic research effort.

INVESTIGATOR-INITIATED PROJECTS

Mr. NATCHER. What will be the role of the investigator-initiated research grant? Will it be de-emphasized, Dr. Goldstein?

Dr. GOLDSTEIN. Sir, it is the single most important mechanism we have. Not only will it not be de-emphasized, to use a double negative, we will continue to give it first priority. It is our most important research tool.

Mr. NATCHER. The 1986 Appropriation Act requires NIH to fund no fewer than 6,100 new and competing research grants. The Administration is asking us to change this language to take out the requirement to fund a certain number of grants. At the same time, as you know, Doctor, the Administration is asking us to include language in the 1987 bill to require NIH and ADAMHA to fund no fewer than 19,400 grants.

You know, Doctor, you have heard about 6,000 grants and 6,100 grants. You know this has been bandied about from year to year. That started on this side, Doctor, on this side.

Now, if you will, give us your views on these two proposals, Dr. Goldstein?

Dr. GOLDSTEIN. Sir, research is in some respects an endless search for better information. The decision of how much research we should do is really a decision much too important for scientists to make. It is a social decision. And it is a decision which I would rather trust the Congress to help us make than to have us as administrators come up with the number.

DOWNWARD NEGOTIATIONS

Now, Doctor, what do you think of the budget proposal which requires downward negotiation of grant costs recommended by study sections generally? How do you feel about it, Doctor?

Dr. GOLDSTEIN. Sir, like my confidence in the Congress, I have confidence in the peer review system.

I sit in a study section meeting, and I know these scientist have their red pencils out, reducing budgets as appropriate all the time. I trust their judgment.

Now, what impact does a cut in a necessary budget have? It does not destroy the research? No, sir, it usually does not. What it often does is it slows it down. Again the decision is whether we slow it down or not? We are generally not discontinuing research, we are usually slowing it down.

Mr. NATCHER. Dr. Goldstein, would you prefer to fund fewer grants rather than cutting the cost of each grant? How do you feel generally about it?

Dr. GOLDSTEIN. If I had my way, sir, I would do everything I do as best as possible. If I had to make a choice personally—this may not represent Dr. Wyngaarden's opinion, I do not know—I would fund fewer grants adequately than more grants inadequately.

Mr. NATCHER. If Congress were to increase your budget, one, would you use the added funds first to more fully fund approved grants or, two, would you prefer to use it to fund more grants and/or, three, would you use it for some other mechanism? Where would you land, Doctor?

Dr. GOLDSTEIN. If you would permit me, I would say all of the above. But if I have to make one choice, I would more adequately fund fewer grants.

LOU GEHRIG'S DISEASE

Mr. NATCHER. You mentioned our old friend, Jake Javits, who suffered from Lou Gehrig's disease, who died last week. He appeared before our Committee on a number of occasions. Doctor, when I got here, Jake Javits was in the House, an able man, an able man in the Senate. I always enjoyed serving with him. I do not know of anyone during my lifetime that suffered like he did and apparently lived with it. And he was a great man. We were awfully sorry to hear on our Committee that he had died, and he was just as kind and considerate, you know, about his requests when he would come in and talk to us. He appeared on a number of occasions.

Doctor, tell us what progress in diagnosis, prevention, or treatment do we have as far as this terrible disease that is known as Lou Gehrig's disease? Where are we, Doctor?

Dr. GOLDSTEIN. I am embarrassed to say not very far. We are making slow but steady progress. We are still working to try to find out what goes wrong, why do cells in this very one part of the nervous system die, why are they more vulnerable and why do they die when cells right next to them live happily and function? These cells constitute the motor system.

We do have a theory at the moment which seems the most likely, but we have a long way to go before we demonstrate it to be true. The nerve cell has a body and then a long process which connects to a muscle or another part of the body, most often a muscle; particularly in the case of ALS, a muscle.

Remember, it is the longest cell in the body. With most cells we must have a microscope to see the beginning and the end. But here we have a single cell that may be as long as the whole spinal cord. That is a whole meter in length.

The cell is dependent upon a very delicate transport system. It is like a large canal. Materials are produced at one end of the cell. Neurotransmitters are substances that control the life of the muscle that it innervates. These materials are produced in the cell body in the brain and transmitted all the way down the spinal cord by one cell.

What we find in Lou Gehrig's disease is an interruption of that transport. The materials are not getting down to the working end and other materials not returning to the cell body. Why are they not getting down to the working end? If we could answer that, I think we could develop some ways of intervening. There seems to be a blockage of transport in the canal. Why? We do not know.

Our progress is slow, but I can assure you we are giving it priority attention.

JAVITS AWARD PROGRAMS

Mr. NATCHER. Doctor, you are supporting, I believe, 147 Javits Scholars.

Just briefly, what is this program, Doctor? I believe you have four centers too.

Dr. GOLDSTEIN. That is right, sir.

Mr. NATCHER. Tell us briefly now what we have here, Doctor.

Dr. GOLDSTEIN. After discussions with Senator Javits, Senator Javits and I discussed what could we do to take on the most difficult problems in neuroscience, not the ones that are the most easily described and study sections feel most comfortable with, but those that are at the cutting edge of neuroscience.

We jointly agreed that the most important thing we could do is like the Marines, pick a few good men and women. Give them stability so that they did not have to write frequent grant applications.

So we developed a program known as the Javits Neuroscience Investigatorships, which provides a scientist who has already demonstrated his capability, has a track record of productivity, seven years of uninterrupted research support. We urge him to take on the tough questions—not to take on the problems that are easily or more easily solved.

The program gives about 10 percent, the upper 10 percent of our grantees the stability for seven years of research stability based on their track record. That is called the Senator Jacob Javits Neuroscience Investigatorship.

ALZHEIMER'S DISEASE

Mr. NATCHER. Doctor, in the past, you have been quite frank with us about the lack of progress in regard to Alzheimer's disease.

Anything new, Doctor?

Dr. GOLDSTEIN. One very interesting result that I hesitate to report on because the first I read about it was in a Boston newspaper the other day.

We believed at one time that roughly 10 to 15 percent of all patients who had Alzheimer's disease had it on a genetic basis, that it ran in those families. We have done now indepth genetic studies, by the way with a very close collaboration of our scientific colleagues in Italy, in France and Canada, where there are pockets of the disease, where families have not moved, and we can go in and study generations of the family in one area.

We have come up with rather surprising information, that the correct figure is more probably 20 to 30 percent of all patients who have Alzheimer's disease have it on a genetic basis. But let me also give the positive side. That means that 70 to 80 percent do not.

But there is a cluster of this disease, which is probably genetic in origin and the issue is what gene, and what does that gene do? I read in the Boston newspapers two days ago that a very, very capable investigator in Boston had identified a gene associated with the disease and the gene product. He will be giving this report at a scientific meeting, which I and my colleagues will be attending, in the middle of April.

Obviously, until we really see the scientific paper, it is very hard to judge the adequacy of the newspaper report of his findings. But knowing the investigator, I would be very surprised if his results were not reproducible.

Now, I think this is an exciting finding. Perhaps at least one aspect of the disease may be able to be treated in the future through enzyme replacement therapy, or maybe even a technique called genetic engineering. This is one important opportunity.

The second thing is this research is in some respects a very complex jigsaw puzzle. Because for every piece you put in place, you find two other holes that you did not realize were there. What we are now beginning to define are the interrelationships in the neurotransmitter system.

I reported to you a year ago that one neurotransmitter called acetylcholine was probably the basis for disease. Well, we now recognize another one, a substance called somatostatin, which probably may be of equal importance. The progress I am trying to report is that fundamental elements of the disease mechanism are now being dissected. We are at the point where we finally know what the meaningful questions are. I really do not yet know what the answers are.

Mr. NATCHER. Mr. Conte.

FUNDING RATES

Mr. CONTE. Dr. Goldstein, it is a pleasure to see you once again and have you before our Committee.

As we have sat here over the past couple of days and listened to the new treatments in cancer and the tremendous impact research on the cardiovascular system has had on the life expectancy of the American people, I continue to be heartened by the advances made by the biomedical research, by the return of the investment that this Subcommittee has supported, and by improving health of the people in this country and ultimately of the people throughout the world.

Dr. Goldstein, it seems to me that you are riding a crest of two revolutions. The first is the area of genetics, and the second is the area of the brain. And I continue to believe, Doctor, that of any area of research, your is by far the headiest.

Dr. GOLDSTEIN. I do not think it would be appropriate for me to comment, sir.

Mr. CONTE. Doctor, before getting into the specifics, I want to go over some of the budget numbers because they look quite shocking.

From the 1985 appropriation which provided for 722 new and competing grants and in the President's revised budget, that number would fall to 598 new and competing grants.

Dr. GOLDSTEIN. That is right. In FY '86.

Mr. CONTE. And under the FY '87 budget request, the number would be 538 new and competing grants in FY '87, a reduction of nearly 200 grants. Is that correct?

Dr. GOLDSTEIN. That is correct, sir.

Mr. CONTE. And the award rate, the number of scientifically meritorious grants actually funded for the same period would fall from 37.8 percent in FY '85 to 26.7 percent in '86, to 22.5 percent in FY '87, the lowest award rate in the entire NIH and probably in the history of NIH, is that correct?

Dr. GOLDSTEIN. I can say in the history of NINCDS, sir. I am not sure of the figures in the history of NIH.

Mr. CONTE. Doctor, under this scenario, how is it possible to sustain the interest and the excitement of researchers in the field with a 22.5 percent award rate?

Dr. GOLDSTEIN. Very difficult, sir.

Mr. CONTE. And, Doctor, how is it possible to sustain a momentum on one of the most rapidly evolving fields of biomedical science with a 200 drop in the number of new awards?

Dr. GOLDSTEIN. I cannot answer the question, sir.

Mr. CONTE. A justification even at these reduced levels of grants you indicate that the budget for the institute would require 17.4 percent reduction from recommended levels in the size of the awards for new and competing grants in FY '87, is that correct?

Dr. GOLDSTEIN. That is correct, sir.

Mr. CONTE. And a 12.7 percent reduction of full commitment levels for continuation grants, is that correct?

Dr. GOLDSTEIN. That is correct, sir.

Mr. CONTE. What is the average reduction from full commitment levels that has historically been made against new and competing and continuation grants?

Dr. GOLDSTEIN. In new grants, the historical reduction has been approximately 3 percent, and in non-competing grants, historically 1 percent.

Mr. CONTE. What does it do to a grant to have the award reduced by more than 17 percent?

Dr. GOLDSTEIN. At that level, probably some grants will have to be discontinued.

Mr. CONTE. And in centers, your justification states that the reduction from the full commitment level under the FY '87 budget request will be 14 percent, is that right?

Dr. GOLDSTEIN. That is correct, sir.

Mr. CONTE. The only conclusion that I can draw from these figures is that the revised FY '86 budget after the proposed rescissions and the FY '87 budget request will be positively harmful to this institute.

Do you have any reason to dispute my conclusion?

Dr. GOLDSTEIN. No, sir.

HUNTINGTON'S DISEASE

Mr. CONTE. One of the things that really got the ball rolling in the genetic area was the work in Huntington's disease, which set the paradigm for genetic diseases of developing family registries, and using that knowledge to search for chromosomes and for the genetic markers. What is the latest status of the research for Huntington's disease?

Dr. GOLDSTEIN. I have informal information that the group at the Mass. General Hospital, which identified the marker, the area of the chromosome on which the gene exists, I have informal information that they are now very rapidly approaching the identification of the gene itself. And I have been—I do not want to say assured, but advised that within the next few years, we will probably have the gene.

Mr. CONTE. That is good news.

And, last year, when OMB tried to pull its backhanded maneuver to cut back the number of new and competing grants to 5,000 and to do away with some of the centers, one of the most shocking examples of the effect of that maneuver was the fact that the two Huntington Disease Research Centers that helped produce the breakthroughs in Huntington's disease, and genetic disease in general, might very well not have been funded because of the intensity of the competition for the limited number of grants.

What was the final outcome? Both centers were eventually funded, is that correct?

Dr. GOLDSTEIN. That is correct, sir.

For the record, Mr. Conte, I would like to share responsibility with my colleagues in the OMB in this sense. I had to make the decision in terms of available dollars about whether it would be individual research projects or centers. And since my flag is already nailed to the importance of individual research projects, given the two, it was my responsibility and I made the decision to go the route of priority for individual projects under the terms and conditions of the budget at that time.

Mr. CONTE. Well, OK, but I doubt if you had any involvement in the OMB decision that put you in the position of making those difficult decisions.

As a sidelight here, facility construction and renovation after the new NIH reauthorization, do you have any authority for facility construction or renovation?

Dr. GOLDSTEIN. No, sir.

GENETIC DISEASES

Mr. CONTE. One of the benefits of this research is a tremendous promise now held up in all genetic diseases.

You and I, Doctor, were present last spring at the first meeting of a coalition of all voluntary genetic disease organizations. There must have been 300 people there representing numerous voluntary organizations.

How do we take advantage of the promises of genetic research and extend them to the benefit of as many of the genetic diseases that may now be in reach as possible?

Dr. **GOLDSTEIN.** As the Chairman indicated, and as you have reaffirmed, genetic research is one of the most rapidly moving of our methodologies. A very large proportion of all genetic diseases affects that most vulnerable of systems, the nervous system, as it is being developed in utero.

What I am building up to is (a) we have a large number of genetic disorders associated with neurological diseases.

As my opening statement indicated, we have spent five long difficult years training neuroscientists in genetic methodology. They are now available to us. Young people have been trained to use this methodology to answer difficult questions.

What we need to do most for those young people is to give them the opportunity to do the research for which they are trained in an environment in which the neurological diseases exist. And so the mechanisms which we already have available to us, the project grant, the program project grant, the research center, are all really very, very adequate to accomplish our purposes.

NEUROFIBROMATOSIS

Mr. **CONTE.** One of the diseases that I have been following and trying to generate enthusiasm and interest in the research community about to take advantage of these developments is neurofibromatosis.

Dr. **GOLDSTEIN.** Yes, sir.

Mr. **CONTE.** Last year, one of my constituents, Mrs. Claudette Kiely, thanks to the Chairman here, described her family experience of misinformation and misdiagnosis of NF, which is still common today.

What is NINCDS doing to specifically inform physicians and health care workers about NF or elephant disease, or whatever you want to call it?

Dr. **GOLDSTEIN.** This committee urged the Institute in its report last year to give attention to the problem of the present status of diagnosis and of therapy of the patient with neurofibromatosis. And so, sir, in response to the committee's charge, we have organized a national panel of outstanding clinical people in the field to develop a paper which would be published, widely disseminated, and would bring the clinical community as well as the patient community up to date on the questions you are raising.

I would like to submit to you, sir, the names of the committee which have met, which are meeting, and I would hope, within the next three to seven weeks, will honor us with their report.

And, sir, I have one for the Chairman and one for the reporter. This is the membership of the committee which is at work fulfilling the charge.

In the interim, with the information we have available, the NINCDS has a brochure which describes neurofibromatosis, what it is and what we know about it. This is a public information brochure which is widely disseminated, both through our own organization and our colleagues in the national voluntary agency, the National Neurofibromatosis Foundation. If you would care to look at this, sir, this is the brochure.

[The following was received for the record:]

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Working Group on Neurofibromatosis

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FACT SHEET

neurofibromatosis

What is neurofibromatosis?

Neurofibromatosis is a genetic disorder of the nervous system. Characteristic signs in the adult are six or more flat, coffee-colored (café-au-lait) skin spots; multiple, usually benign tumors, called "neurofibromas" when they appear on the nerves; and sometimes curvature of the spine.

How common is the disorder?

No formal system exists for collecting statistics on neurofibromatosis, but the National Neurofibromatosis Foundation estimates that approximately 100,000 Americans, of both sexes and all national origins or races, are afflicted. Each year the disease affects approximately 1 in every 3,000 babies born. This would place neurofibromatosis among the most common hereditary diseases.

What are its signs and symptoms?

Symptoms usually appear in childhood or adolescence, but can occur as late as age 50. Neurofibromatosis patients may develop any one or several of the following problems:

- Many small tumors (nodules) just under the skin;
- Nodules on the iris of the eye in adolescents and older individuals;
- Large pressure-sensitive tumors just under the skin;
- Severe curvature of the spine;
- Enlargement and deformation of bones other than the spine;
- Tumors on the auditory nerves, causing deafness;
- Tumors on the optic nerves, causing blindness in one or both eyes;
- Tumors of the brain or spinal cord;
- High blood pressure in younger people.

What causes neurofibromatosis?

Most cases of neurofibromatosis are inherited from one of the parents, but some result from the spontaneous change (mutation) of a gene. Once a mutation has taken place, neurofibromatosis can be passed on to succeeding generations. How the mutant gene produces neurofibromatosis is unknown.

How is it inherited?

Neurofibromatosis is an autosomal dominant disorder. Each child of an affected parent has a 50 percent chance of inheriting the defective gene and developing neurofibromatosis.

What are the early signs?

Children with neurofibromatosis can almost always be identified shortly after birth by the appearance of light-brown spots on their skin. Physicians generally consider that any young child with five or more such "café-au-lait" spots, each half a centimeter or more in diameter, has neurofibromatosis. Characteristic tumors may appear on the nerves and elsewhere in the body during childhood, but usually do not develop until early adulthood.

What forms does neurofibromatosis take?

Neurofibromatosis has been classified into two somewhat overlapping types: peripheral and central with bilaterial acoustic neuromas.

Peripheral neurofibromatosis—This type is characterized by six or more café-au-lait spots, many small tumors, and a network of larger tumors under the skin. Enlargement and deformation of bones and other parts of the body may occur. Severe left-right curvature of the spine (scoliosis) is common. Occasionally tumors may develop in the brain, cranial nerve, or spinal cord.

Central neurofibromatosis with bilateral acoustic neuromas—This type is characterized by multiple tumors on the cranial and spinal nerves, and by other lesions of the brain and spinal cord. Tumors of both auditory nerves are the hallmark, with hearing loss beginning about age 20 generally the first symptom.

Do benign tumors ever become malignant?

Yes, in about 3 to 5 percent of all cases.

Is there any treatment for neurofibromatosis?

Not for the disorder itself, but there are treatments aimed at controlling symptoms. Bone malformation, particularly scoliosis, is treated by surgery, a back brace, or both. Auditory or optic nerve tumors can be treated by surgery, but if nerves on both sides are affected, the risks may be greater than the benefits. Painful or disfiguring skin tumors can be removed by surgery, but there is some danger that they will grow back in greater numbers.

Do neurofibromatosis patients lead normal lives?

In most cases, symptoms are mild and patients live completely normal and productive lives. In its more severe forms, however, neurofibromatosis can be devastating and debilitating.

Is there a prenatal test?

For those who are affected by neurofibromatosis, the decision to have or not to have children can be a difficult one. There is currently no prenatal test to determine if an unborn child is affected by neurofibromatosis. A genetic counselor can offer support and guidance to couples faced with the childbearing decision.

What research is being done?

The National Institute of Neurological and Communicative Disorders and Stroke, a part of the National Institutes of Health (NIH), is studying genetics and cell growth in neurofibromatosis patients. In 1979, a weekly research clinic was begun at NIH to study patients and families with the disorder; referring physicians retain responsibility for the care and treatment of their patients. Research is also being carried on at several large medical centers in the United States. Scientists are conducting clinical studies on the diagnosis and treatment of neurofibromatosis. Investigators are also trying to locate the mutant gene that causes the disease. Other scientists are studying the role of hormones and growth factors in the development of neurofibromatosis.

How can I help research?

The National Institute of Neurological and Communicative Disorders and Stroke and the National Institute of Mental Health support two national human specimen banks, one at the Wadsworth Veterans Administration Hospital in Los Angeles and the other at McLean Hospital near Boston. These banks supply investigators around the world with tissue from patients with neurological and psychiatric diseases. Both banks need tissue from neurofibromatosis patients to enable scientists to study this disorder more intensely. Prospective donors should write to:

Dr. Wallace W. Tourtellotte, Director
Human Neurospecimen Bank
VA Wadsworth Hospital Center
Los Angeles, CA 90073
Telephone: (213) 824-4307 (Call collect.)

Dr. Edward D. Bird, Director
Brain Tissue Bank, Mailman Research Center
McLean Hospital
115 Mill Street
Belmont, MA 02178
Telephone: (617) 855-2400 (Call collect 24 hours a day.)

Where can I get medical care?

Physicians who specialize in diagnosing and treating neurofibromatosis may be contacted through university medical centers. In addition, the following centers have neurofibromatosis clinics:

- Massachusetts General Hospital, Boston, Mass.
- Mt. Sinai School of Medicine, New York City
- Children's Hospital, Philadelphia, Pa.
- Children's Hospital National Medical Center, Washington, D.C.
- Baylor School of Medicine, Houston, Tex.

Where can I get more information?

Information for patients, families, and physicians is available from:

National Neurofibromatosis Foundation, Inc.
70 West 40th Street
4th Floor
New York, NY 10018
(212) 869-9034

The foundation was chartered by the State of New York in 1978 as a nonprofit organization. Its purposes are to provide neurofibromatosis patients and their families with information about the disease and to help them find medical, social, and genetic counseling. The foundation also provides information on neurofibromatosis to health professionals and supports scientific research on the disease.

For information about the NIH Neurofibromatosis Clinic, write:

Coordinator, Inter-Institute Genetics Program
Building 10, Room 1D21
National Institutes of Health
Bethesda, MD 20205
(301) 496-1380

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U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

Those are the two steps we are taking to be responsive to the need of the public and of practicing clinical persons for clinical information about the disease.

Mr. NATCHER. Thank you. Mr. Early.

SEQUESTRATION AND RESCISSION

Mr. EARLY. Thank you, Mr. Chairman. Dr. Goldstein, your Institute had $18,570,000 sequestered, is that right?

Dr. GOLDSTEIN. The $18.6 million was sequestered.

Mr. EARLY. Now you come in with a $9.5-million rescission?

Dr. GOLDSTEIN. That is the rescission which has been placed on the Institute.

Mr. EARLY. How was that arrived at? Who did that?

Dr. GOLDSTEIN. I really don't know, sir.

Mr. EARLY. It was not you?

Dr. GOLDSTEIN. No, that was the figure that was given to me, sir.

Mr. EARLY. That was given to you? You are the Director of the Institute.

Dr. GOLDSTEIN. That is correct sir.

Mr. EARLY. So you had no choice on rescission? Where are you going to get the money if we accepted the rescission?

Dr. GOLDSTEIN. We would cut back on our activities.

Mr. EARLY. What activities? I would think you would have a game plan when you send up a rescission, you must know what you are going to do.

Dr. GOLDSTEIN. I do have a game plan, sir. We will cut further every active research project. Remember, the rescission itself——

Mr. EARLY. Across the board cut?

Dr. GOLDSTEIN. Well, no. One by one, sir. We do not do anything across the board.

HUNTINGTON'S DISEASE AWARD

Mr. EARLY. I heard your response to Mr. Conte. With regards to Huntington's disease, did you recommend that they cut out the group in Boston?

Dr. GOLDSTEIN. When the budget was made available to me, as the responsible Officer of the Institute, I had to make a decision, within the budget that was made available, as to how best to spent it in the interests of neurological research.

Mr. EARLY. Doctor, be brief in your answers please.

Dr. GOLDSTEIN. I made the decision to fund individual research projects rather than centers.

INSTITUTE LEADERSHIP

Mr. EARLY. That is one of the big problems I have. OMB is now running the Institutes. I have seen some Directors stand up and fight and some do not. Did you go along with the multi-funding idea?

Dr. GOLDSTEIN. Sir, I run the NINCDS. I am responsible for it and I run it.

Mr. EARLY. That is your judgment. I think OMB runs it.

Dr. GOLDSTEIN. I run it within the resources made available to me by the Congress and by the President.

Mr. EARLY. But, from what you told the Chairman, as far as research reductions, I get the impression that you can absorb them. You say all it will do is slow down research. In my 12 years, I have not seen any progress on spinal cord research at all, Dr. Goldstein. That is frustrating. You spoke of the Alzheimer's disease article that you read it in the Boston Globe. I mean, if it is an exciting thing, I would think your Institute would be on top of it.

Dr. GOLDSTEIN. We are on top of it.

Mr. EARLY. You are going to wait until next month when you go to a meeting to find out what Dr. Saiko has to say?

Dr. GOLDSTEIN. That is the accepted national and international way of the transmission of scientific information, sir.

FUNDING RATES

Mr. EARLY. What is your payline under the 1986 revised budget Doctor?

Dr. GOLDSTEIN. One-five-zero, sir.

Mr. EARLY. What would it be under the 1987 budget?

Dr. GOLDSTEIN. One-four-zero, sir.

Mr. EARLY. That is acceptable to you Doctor?

Dr. GOLDSTEIN. Within the resources I have, I have no choice.

Mr. EARLY. What about the downward negotiation? It's almost 18 percent, Doctor.

Dr. GOLDSTEIN. That is correct, sir.

Mr. EARLY. You said to Mr. Conte that we would probably have to drop some.

Dr. GOLDSTEIN. That is correct.

Mr. EARLY. How many do you anticipate dropping?

Dr. GOLDSTEIN. I would dare say something in the order of magnitude of from two to up to four dozen. Investigators will tell us they cannot conduct the research for which they are responsible with that degree of cuts.

Mr. EARLY. Can you provide for the record who you think they will be, please?

Dr. GOLDSTEIN. Yes, sir.

[The information follows:]

TERMINATION OF GRANTS

When actual funds awarded are reduced from approved levels on the order of 17 percent, it is likely that the awarded funds will be insufficient for certain grantees to continue their research. Under these circumstances, the decision to terminate a grant is a decision properly made by the investigator and the institution involved. Since these circumstances have not yet arisen, it is not possible to identify specific investigators who might request termination. However, there are three categories of grants with special characteristics that make them more likely to terminate than continue at a reduced level. The first category is clinical trials which are vulnerable because they are conducted in accordance with very strict protocols and patient requirements. A second category is the New Investigator Research awards which provide a maximum of $50,000 to first-time applicants for research grants. This level of support is a relatively modest amount and reductions may undermine the viability of some of these projects which could lead to a request for termination. A third category is the Positron Emission Tomography research centers. The costs for maintaining the equipment in these centers is very high. The use and operation of the PET equipment require a large team of support staff so that the research investigators may maximize the benefits of this technology. A reduction in funds could imperil both the maintenance of the equipment and the salaries and expenses for the support staff and lead an institution to request termination of the grant.

NEURONAL REGENERATION

Mr. EARLY. Doctor, on the chart that you had up there, what was that—neurono-regeneration?

Dr. GOLDSTEIN. Neuronal, like nerve cell.

Mr. EARLY. You said that we were going to have something in three years?

Dr. GOLDSTEIN. That is correct, sir.

Mr. EARLY. Why? How are we going to get the three? What study is going on or what clinical trial is going to give us the results?

Dr. GOLDSTEIN. We have, at the present time, four spinal cord injury research centers in which these studies are the major focal point. Namely, the development of the methodology to get the central nervous system to regenerate its lost parts.

Mr. EARLY. So, you have four going on now?

Dr. GOLDSTEIN. That is correct, sir. Four centers.

Mr. EARLY. Will any of them have to take cuts because of these reductions?

Dr. GOLDSTEIN. Yes, sir They will absorb about a 14 percent cut in 1987.

Mr. EARLY. Is that going to defer the result from three years to even more years?

Dr. GOLDSTEIN. It is part of my three year plan. In other words, the three years that I spoke to you about, is at the level of the President's budget for 1987.

Mr. EARLY. Will the conclusion still be available in three years?

Dr. GOLDSTEIN. Yes, sir. Given the projection of the President's budget for 1987, and the impact it has on this type of research program, it will now take about three years to get these results.

Mr. EARLY. Is that progress? Are we saving money, Doctor, when you slow down research?

Dr. GOLDSTEIN. In the long run, it will cost us more money than we are saving.

FLEXIBILITY

Mr. EARLY. So, therefore Doctor, from your comments, you evidently are not concerned about the loss of flexibility or independence in your Institute?

Dr. GOLDSTEIN. I have not lost flexibility. I have lost resources.

Mr. EARLY. Some of the other Directors we had in here the other day were upset with it. I was really pleased that they admitted they were kind of upset with it.

Doctor, is your Institute turning any money over to the Assistant Secretary's office?

Dr. GOLDSTEIN. $1.5 million, sir.

Mr. EARLY. $1.5 million. And that is not going to affect your flexibility at all?

Dr. GOLDSTEIN. The $1.5 million is in support of the AIDS brain research projects we are presently doing.

Mr. EARLY. That was not my question to you. My question to you was: was it going to affect your flexibility at all?

Dr. GOLDSTEIN. I happen to have great faith in the Assistant Secretary.

Mr. EARLY. Well, good for you. Doctor, you have $18½ million sequestered, you have a $10 million rescission, and you have $1½ million going over to the Assistant Secretary's office. How can you have flexibility with no money Doctor?

Dr. GOLDSTEIN. Innovative management, sir.

Mr. EARLY. We would have a lot more breakthroughs if we had that kind of management Dr. Goldstein.

Dr. GOLDSTEIN. Additional resources would clearly accelerate the important programs we are supporting.

CLINICAL TRIALS

Mr. EARLY. Will you curtail any of the ongoing clinical trials with the 1986 revised budget?

Dr. GOLDSTEIN The 1986 revised budget permits us to continue the trials we have already initiated.

Mr. EARLY. So, you are not going to curtail any?

Dr. GOLDSTEIN. We are not going to cut those back at all.

Mr. EARLY. Just answer me no. I would appreciate it, Doctor.

Will you have to curtail any ongoing clinical trials with your budget request?

Dr. GOLDSTEIN. In 1987 we will not initiate any new additional clinical trials.

Mr. EARLY. My question: were you going to curtail any ongoing clinical trials?

Dr. GOLDSTEIN. No, sir.

Mr. EARLY. Fine.

Will you be able to start any new clinical trials in 1987?

Dr. GOLDSTEIN. None at all, sir.

Mr. EARLY. Are there any high priority clinical trials which are ready but cannot be initiated because of a lack of 1987 funds?

Dr. GOLDSTEIN. There will be nine of the highest priority that we cannot initiate.

Mr. EARLY. That does not bother you, Doctor?

Dr. GOLDSTEIN. I am very distressed.

Mr. EARLY. In your remarks, you suggested how good OMB is doing with this budget.

Do you have a few examples of how the Institute utilizes its research and development contract mechanism.

Dr. GOLDSTEIN. Our contract mechanism is used primarily for what we call research and development. There are two programs that illustrate this. The first is our Antiepileptic Drug Development Program. This is a program in which new chemicals are screened for their possibility as new anti-epileptic medication. This is a screening process. The drug companies provide us the chemicals out of their laboratories, and we do the toxicity testing. Once they are defined as non toxic, then the drug companies join us in responsibility for clinical testing. Clinical in the sense of paying for the clinical trial.

The second program that we use our funds for——

Mr. **Early**. Do you have any input in that?

Dr. **Goldstein**. Input in what respect, sir?

Mr. **Early**. In the trial—at that stage—where the priorities——

Dr. **Goldstein**. Yes. We monitor the design of the clinical trial itself and monitor the results of the trial. But, it is a drug company product. This is part of our interaction with industry.

PARKINSON'S DISEASE

Mr. **Early**. What specific research do you have going on with regards to Parkinson's disease today, Doctor?

Dr. **Goldstein**. Oh, very, very exciting in two separate areas.

The first is, there is a street drug, a tailor-made drug called MPTP. This drug is made in some people's basements, and, taken for kicks. It turns out that the drug destroys that one, very small area of the brain, we call the black substance—substantia nigra—that small area of the brain whose destruction is responsible for Parkinson's disease. We have taken that drug and with its use been able to develop a reliable animal model. We have never had an animal model of Parkinson's disease to be able to test therapy on before we went to humans. The animal models we used before were not very good.

Mr. **Early**. How much was spent on Parkinson's disease in 1985?

Dr. **Goldstein**. $18½ million.

Mr. **Early**. Well, you cannot tell me how much will be spent in 1986, because you do not know what the rescission is going to be. It was made by someone else. It was put together by someone else, but acceptable to you. But, it was put together by someone else.

How much are you going to spend on Parkinson's disease this year?

Dr. **Goldstein**. In 1986?

Mr. **Early**. Yes.

Dr. **Goldstein**. Under the Sequestration Act, $19.436 million.

Mr. **Early**. And, how much do you have in your 1986 budget?

Dr. **Goldstein**. $18.787 million.

Mr. **Early**. So, you just said we had some exciting things going on regarding Parkinson's disease, but we are going to spend less than we spent last year.

Dr. **Goldstein**. Yes, sir.

Mr. **Early**. One final question. No, I have no more questions.

Mr. **Natcher**. Now, Doctor, tell us about research developments with respect to Parkinson's disease. What can you tell us this year, Doctor, that you could not last year?

Dr. **Goldstein**. We now have an acceptable animal model close to man, a chimpanzee, that replicates all of the symptoms of Parkinson's disease. In that animal, sir, we have done a brain implant. The process I described to the committee before. The animal makes an excellent recovery.

SPINAL CORD INJURY

Mr. **Natcher**. Have you anything new to report to us regarding treatment of spinal cord injuries, Doctor?

Dr. GOLDSTEIN. We are presently conducting a controlled clinical trial of a drug. It appears that when the spinal cord is injured, the first four hours after injury is the critical—are the critical hours. After that, the horse is out of the barn. The nerve cell decides within that four hours whether it is going to live or die. We have a drug, Naloxone, which is now under controlled clinical trial in humans, in several institutions, to find if we can protect the spinal cord during those critical four hours. Since it is a blinded trial—blinded in the sense that only the statisticians know what the patient is getting—at this moment I cannot report the results of the trial.

EPILEPSY

Mr. NATCHER. Doctor, are we giving adequate attention to research on epilepsy?

Dr. GOLDSTEIN. I am having a little difficulty with the term adequate attention.

We are giving a great deal of attention to research on epilepsy. There are other epilepsy research activities that could be supported.

Mr. NATCHER. Any new developments, Doctor?

Dr. GOLDSTEIN. Two important issues have come to our attention.

The first, the most common cause of epilepsy south of the U.S. border, is a worm infestation of the brain. It is part of the pork-tapeworm story. Little tapeworms, if I can use that term, infest the patient's brain and the patient develops epilepsy. Again, the most common cause south of our border—we never worried much about it, figuring that it did not happen that often in the United States. Now in our southern states, Texas, New Mexico, Arizona and southern California, patients are showing up in hospitals regularly with this infection called cysticercosis of the human brain.

With the collaboration of the Pan American Health Organization, our Institute and our colleagues in the National Institute of Allergy and Infectious Diseases, are now trying to see whether we can develop a vaccine to protect our public in the southern states against this. We have hope that such a vaccine is possible.

The second issue is traumatic epilepsy. A great deal of epilepsy is secondary to blows to the brains of children and adults. Right at the moment, we have a controlled clinical trial being done in Los Angeles, particularly, in a black population, in order to see if we can prevent epilepsy after a blow to the head.

STROKE

Mr. NATCHER. Doctor, in your statement, you cite advances with respect to treatment of stroke. Are these findings well understood by medical practitioners—is this information being distributed?

Dr. GOLDSTEIN. Yes, indeed. Very widely distributed. Yes.

POST-POLIO SYNDROME

Mr. NATCHER. How much attention are you giving to the problem of people who have had polio and are having a recurrence of symptoms years later—some 20 years later, maybe, 25, 30 years later. What about this, Dr. Goldstein?

Dr. **Goldstein**. Yes, sir. This is called the post-polio syndrome in which patients who have had polio, recovered and returned to work, 20 years later, have a sudden, unexplained loss of their muscle strength and control. The great danger that we feared was that the patient had a resurgence of polio. We are quite certain that is not true.

The principle we are presently working on, one I showed you on the chart, was called "sprouting." After the patient has had polio and recovered, these nervous system sprouts occur. We believe these sprouts are very delicate, and with over-use they die.

There are presently a number of projects, including a major one in our own NIH laboratory, trying to find out if that is true.

OMB

Mr. **Natcher**. Doctor, in answer to one of Mr. Early's questions in regard to OMB, I liked your answer, Doctor. I liked your answer. OMB, I do not think, is running your department. I do not think they are running any of the institutes out there. Mr. Early has a lot more to do with that than they do.

If you would attend the markup and sit at that table with Joe Early and all the rest of us, you would find out that he has a whole lot more to do about it than they do. I am in favor of that because I help him in cases when he needs help.

But, Doctor, I liked your answer. Is it true that OMB is now apportioning your funds into 14 categories? We hear something like that. Is any part of that true?

Dr. **Goldstein**. It is my understanding the Congress apportions my funds.

Mr. **Natcher**. Well, that is good. That is the way it should be, Doctor, and do not change your mind.

DR. PETROFSKY

Now, Doctor, from time to time, publicity is given to Dr. Petrofsky's work with crippled patients at Wright State University in Dayton, Ohio. We have talked with you about this before. Again, several weeks ago on 60 Minutes I saw the program. I have seen that program once or twice.

Any change in this situation, Doctor?

Dr. **Goldstein**. It is moving ahead very rapidly in Dr. Petrofsky's laboratory and in three other laboratories in this country.

I must say, sir, most of the support comes from two organizations: The National Institute of Handicapped Research and the Veterans Administration. We are providing funds for research on the development of the improved electrodes and improved microcomputers that are plugged into the stimulation system.

So in that respect, we are doing the basic research, and our sister agencies are applying it to the specific ambulatory problem of the paraplegic.

Mr. **Natcher**. Doctor, as you probably know, one of our representatives in the House, Tony Hall, one of the able members of the House, represents Dayton.

Dr. **Goldstein**. Yes, sir.

Mr. **Natcher**. He comes in and talks to us from time to time about this. I am glad to have your answer, Doctor, and I know you are following it and that you will follow this investigation and this research that is being done along this line.

Mr. Hoyer, I yield to you at this time.

Mr. **Hoyer**. Thank you very much, Mr. Chairman.

Doctor, first of all, I want to welcome you to the Committee again and say what an excellent job I think you are doing. I am sure that has been said by the Chairman and Mr. Early. Mr. Early has told you if he can get you some dollars to do your job, things will be better, I am sure.

RETT'S SYNDROME

Rett's syndrome, Doctor.

Dr. **Goldstein**. Yes, sir.

Mr. **Hoyer**. You know I am very interested in that, realizing there is a relatively small constituency, but an important constituency, an important affected group.

I have received the report on Rett's syndrome prepared by your institute and the National Institute of Child Health and Human Development. It highlights the fact that the two institutes cofunded a conference at Johns Hopkins Medical School last fall.

The report suggests that the current mechanisms at NIH will be used to address this syndrome in a multidisciplinary study or through individual research grants. Doctor, how successful do you believe the international workshop was? And how were the responsibilities for the report divided?

Dr. **Goldstein**. Well, one, it was a most successful workshop, far exceeding even our own expectations. It clearly delineated that this is a real disease and not just a change in name of a recognized disease.

The second thing it demonstrated is in a broader area, cerebral palsy. Many of these children in the past were placed under that general term, "cerebral palsy." And, of course, what we are now doing, and this is one excellent example of it, is continuing to define within the general term, cerebral palsy, specific diseases. Cerebral palsy is just the name of a syndrome, a way of describing a group of symptomatologies.

The report was primarily prepared by our colleagues at Johns Hopkins who ran the symposium. Then, our own staff and the staff of the National Institute of Child Health and Human Development worked with the Johns Hopkins group after they completed the scientific part of the report trying to define what the opportunities were. That is the basis of the report.

Mr. **Hoyer**. OK. Thank you, Doctor.

Now that report states that your institute issued an announcement encouraging submission of research grant applications.

Dr. **Goldstein**. Yes, sir.

Mr. **Hoyer**. What has been the response?

Dr. **Goldstein**. So far, very little, but it is very early in the solicitation process. This is a tough research problem, one that people need to think about very carefully; for example, what protocols they can put together which would give meaningful information.

I anticipate, and this is a guess now, Mr. Hoyer, that we will have before the year is out 6 to 12 specific research grant applications attempting to address that research. But I do not know that yet.

Mr. HOYER. Will they apply to both institutes?

Dr. GOLDSTEIN. The answer is yes. We have a mechanism at the NIH we call dual assignment, in which, when an application is clearly of responsibility of more than one institute, it is assigned to both. The investigator gets the best of the deal; namely, whichever institute is able to fund it, has the application.

The application goes through the scientific merit process, which is common for both institutes. Then, whichever institute has the money pays it. So the investigator will get the best of both options.

Mr. HOYER. Whichever institute has the money?

Dr. GOLDSTEIN. Yes, sir.

Mr. HOYER. Which institute is that? We have not had the institute that has the money come before us yet. [Laughter.]

Dr. GOLDSTEIN. Sir, I will be able to respond after the Congress appropriates.

Mr. HOYER. I think that is as good an answer as I am going to be able to get. I agree with that.

I think you have answered that, and I thank you for the attention that has been given. I know those individuals who have been personally affected and involved and who very much felt that this was a separate, identifiable, discrete problem. They feel vindicated in their thoughts. You have just reiterated that as well. I know they will be happy to hear that.

Dr. GOLDSTEIN. They were absolutely correct.

HUNTINGTON'S DISEASE CENTERS

Mr. HOYER. This will be my last series of questions. Let me ask you about the Huntington's disease centers.

Have there been any advances in our understanding of Huntington's disease?

Dr. GOLDSTEIN. Yes, sir. I did tell the Chairman.

Mr. HOYER. Well, if it is already on the record, I apologize.

Dr. GOLDSTEIN. It is on the record.

Mr. HOYER. We need not repeat that.

Did you specifically say how the sequestration was affecting the Harvard Center in that response?

Dr. GOLDSTEIN. No. We were talking about the center grant at Massachusetts General Hospital. Under sequestration, it will be reduced. I do not believe that grant has quite come up yet for its award out of 1986 funds. It will be reduced about ten percent.

Mr. HOYER. Ten percent?

Dr. GOLDSTEIN. Yes, sir.

Mr. HOYER. Now, how does the fiscal '87 budget affect it?

Dr. GOLDSTEIN. It would be reduced about 17 percent.

Mr Hoyer. A total of 27 percent?

Dr. GOLDSTEIN. Over two years.

Mr. **Hoyer**. Let me ask you about the Hopkins Center. What is your prognostication for its future?

Dr. **Goldstein**. Again, it has a five-year commitment which we will clearly honor because of its excellent productivity. It will be reduced somewhere in the ballpark figures I gave you previously. I happen to remember the Massachuesetts General Hospital figures specifically, but we do negotiate each one individually. It will be something close to that but probably not the same.

Mr. **Hoyer**. In the neighborhood of a 25 percent cut over two years?

Dr. **Goldstein**. Exactly. Over a two-year period.

Mr. **Hoyer**. Thank you very much, Mr. Chairman.

Thank you, Doctor.

Mr. **Natcher**. Mr. Early?

BUDGET REQUEST FOR 1987

Mr. **Early** Thank you, Mr. Chairman.

Doctor, what was your budget request to PHS?

Dr. **Goldstein**. For 1987, sir?

Mr. **Early**. Yes.

Dr. **Goldstein**. My budget request was made to the NIH, sir, to the director of NIH. In 1987, the budget I requested was $577.2 million.

Mr. **Early**. So it was cut, reduced from your original request by maybe 40 percent?

Dr. **Goldstein**. About that, yes, sir.

Mr. **Early**. Would you provide a list of all the things that were cut by the reduction from your $577.2 million.

Dr. **Goldstein**. The President's budget, yes. All the research activities that I described we will not do are a result of the differences in those budgets.

Mr. **Early**. That is right. All I am asking is that you provide for the record the difference between the $577 million and the $399 million. Tell us what will not be included.

Dr. **Goldstein**. Yes, sir.

[The information follows:]

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological and Communicative Disorders and Stroke

1987 Budget Reductions

The total NINCDS 1987 request to the NIH was $577,229,000. The 1987 President's budget is $399,351,000, a reduction of $177,878,000 from the amount requested. The following are the activities which were reduced.

(In thousands of dollars)

	1987 Request to NIH	1987 President's Budget	Difference from 1987 Request to the 1987 President's Budget
	Amount	Amount	Amount
Research Grants			
Research Projects:			
Noncompeting projects..........	$184,218	$188,941	+ $4,723
Administrative supplementals...	666	668	+ 2
Competing projects............	238,880	80,126	-158,754
Subtotal, research projects..	423,764	269,735	-154,029
Research Centers:			
Specialized/comprehensive ctrs.	32,800	26,371	- 6,429
Subtotal, research centers...	32,800	26,371	- 6,429
Other Research:			
Research career programs.......	12,850	11,872	- 978
Cooperative clinical research..	2,500	957	- 1,543
Minority biomedical support....	250	191	- 59
Other research related.........	2,500	1,892	- 608
Subtotal, other research.....	18,100	14,912	- 3,188
Total, Research Grants.........	474,664	311,018	-163,646
Training			
Individual awards..............	6,128	4,307	- 1,821
Institutional awards...........	8,910	8,280	- 630
Total, Training..............	15,038	12,587	- 2,451
Research & Development Contracts.	16,100	11,529	- 4,571
Intramural Research.............	53,327	47,804	- 5,523
Research Management & Support....	18,100	16,413	- 1,687
TOTAL....................	577,229	399,351	-177,878

Mr. **Early**. Dr. Wyngaarden, what was your budget request for this institute to OMB?

Dr. **Wyngaarden**. The Department's request to OMB was $481.9 million for this Institute.

INDIRECT COSTS

Mr. **Early**. And I understand, Mr. Williams, you corrected the comments you made this morning about indirect costs. What is the adjustment in the '86 budget? Do you have a number on that?

Mr. **Williams**. What I clarified this morning was that those institutions that have an indirect cost rate above 26 percent would in fact potentially lose money. The total NIH budget for whatever savings that might accrue from that, but that would be available. Those savings in indirect cost would be available to the NIH to pay for direct research costs or whatever.

Mr. **Early**. The reduction is not going to go into the saving?

Mr. **Williams**. Not in '86. We did not reduce the budget, the total NIH budget for any savings that might result from applying that proposal in 1986. In 1987, we did.

Mr. **Early**. I see. But will not the universities be told they are not going to get *X* dollars, they are going to get *x* minus the rate from whatever it was to the 26 percent?

Mr. **Williams**. In that particular category, they would potentially lose money. Now, they might, in any given case, get more money for direct research to make it up; they might not. There are other elements of indirect cost such as operations and maintenance. Those categories, we are not proposing to cap those. Those might increase.

So it is hard to tell in any given case what the absolute amount would be, but there would be potentially a reduction in those cases.

Mr. **Early**. Do we not identify the elements? I mean, for every three dollars isn't two for direct cost and one for indirect costs? Is that not the formula you use over at NIH?

Dr. **Wyngaarden**. I think it comes out to be about 50 percent of the direct cost, about 32, 33 of the total cost. These are all averages. So it is about two to one, as you stated.

SENATOR JAVITS RESEARCH CENTERS

Mr. **Early**. Dr. Goldstein, did you say we have four Jacob Javits Neuroscience Centers?

Dr. **Goldstein**. That is correct, sir.

Mr. **Early**. I thought we funded five last year.

Dr. **Goldstein**. No. We ended up funding four.

Mr. **Early**. Was it congressional?

Dr. **Goldstein**. The language was "up to five," sir.

Mr. **Early**. And how much of a cut are they taking?

Dr. **Goldstein**. In 1986, they will take a ten percent cut.

TRAINING

Mr. **Early**. In one of your earlier comments, you said we were doing so much research because we have been able to continually train researchers.

Dr. GOLDSTEIN. That is right, sir.

Mr. EARLY. What does this budget do to your training program?

Dr. GOLDSTEIN. The training program, under sequestration, was reduced by approximately $600,000.

Mr. EARLY. What is the effect going to be? Just slow it down?

Dr. GOLDSTEIN. A number of young people will not receive training. They will not be admitted to training.

Mr. EARLY. Well, are we going to get the rollercoaster effect, because young people are not certain of whether to go into the field or not.

Dr. GOLDSTEIN. Yes, sir.

CONTRACTS

Mr. EARLY. Doctor, with the '87 budget request, you will be supporting only 60 R&D contracts?

Dr. GOLDSTEIN. That is correct, sir.

Mr. EARLY. And how many did you have in '85?

Dr. GOLDSTEIN. Seventy-six, sir.

Mr. EARLY. Seventy-six. So we are going to reduce it 16. What effect will this have on your research initiatives?

Dr. GOLDSTEIN. It will cut down the activity in both the drug development program and the neuroprosthesis program very specifically.

Mr. EARLY. If we continue in this declining direction, in your professional opinion, are you concerned?

Dr. GOLDSTEIN. I will close both programs.

Mr. EARLY. You would close them.

I have no further questions, Mr. Chairman.

Mr. NATCHER. Mr. Hoyer, any additional questions?

Mr. HOYER. Just one if I might, or two.

EPILEPSY

First of all, last year your institute issued a program announcement in basic mechanisms of epilepsy.

Dr. GOLDSTEIN. That is right, sir.

Mr. HOYER. Has the institute awarded any grants in response to this specific program?

Dr. GOLDSTEIN. These applications are coming before our council at the next meeting, sir.

Mr. HOYER. Okay.

Dr. Goldstein. The answer to your question is no, we have not yet awarded these grants.

NEW ANNOUCEMENTS

Mr. HOYER. Will there be any new announcements this year, or will you just be considering those resulting from the——

Dr. GOLDSTEIN. This year is closed. Since the process takes six to nine months and the fiscal year would be over, there will be no additional announcements this year for this year's spending. Does that answer your question?

Mr. HOYER. Yes.

GRANT AVERAGE COST REDUCTIONS

Last question: Your justification states that the average cost, and this may have been covered, if it is, you do not need to review it again, the average cost of the 538 new and competing grants proposed to be funded in 1987 will be 148,930, which is a decrease of 17.4 percent.

Dr. GOLDSTEIN. That is right, sir.

Mr. HOYER. From the fully recommended level. It is my understanding that the average historical reduction has been one percent.

Dr. GOLDSTEIN. That is right, sir.

Mr. HOYER. Now, would you describe the effect of this so-called negotiated reduction, totaling 42 million as outlined in the justification, will have on individual research awards?

Dr. GOLDSTEIN. The speed of which the research will be approached or addressed will be cut proportionately. It will not discontinue the research. In '87, as I mentioned to Mr. Early, a number of projects will have to be discontinued because they could not absorb those cuts.

Mr. HOYER. Thank you, Doctor. Let me say again, Mr. Early, in my opinion, is the real expert in this area. He spends an awful lot of time doing his homework, and he has done it for many years. Clearly, on our Committee, along with the Chairman and Mr. Conte, he is the expert in this area. I rely on him a great deal for advice and counsel. His questions are pretty incisive, and I want to say that I think you have given as direct and responsive answers as we have had during the course of these hearings. I think it is helpful to the Committee.

Dr. GOLDSTEIN. Thank you.

Mr. HOYER. Thank you, sir.

Thank you, Mr. Chairman.

Mr. NATCHER. Mr. Early, any additional questions?

Mr. EARLY. No further questions.

Mr. NATCHER. Dr. Goldstein, we want to thank you and your associates for appearing before our Committee at this time on behalf of your budget request for Fiscal Year 1987.

Doctor, this has been a good hearing, and we appreciate it.

Dr. GOLDSTEIN. Thank you for the opportunity to meet with you, sir.

Mr. NATCHER. Thank you.

The Committee will now adjourn until 10:00 in the morning.

[The following questions were submitted to be answered for the record:]

NEUROGENETIC DISORDERS

Mr. Conte. One of the actions of the Institute of great interest and hope to that group as well as many others was the solicitation you put out last year on the establishment of the multi-disciplinary centers for the study of neuro-genetic disorders of infancy and childhood. What can you tell us about this competition and the establishment of these centers?

Dr. Goldstein. In July 1985, the NINCDS issued a program announcement for the establishment of multidisciplinary research centers to undertake basic and clinical investigations into the etiology, pathogenesis, diagnosis, prevention and therapy of neurogenetic diseases of infancy and childhood, particularly those whose metabolic defect is unknown. So far three applications have been received in response to this announcement, and are currently under scientific merit review. The proposed multidisciplinary research center(s) should provide the necessary milieu where a spectrum of these neurogenetic disorders can be investigated.

Mr. Conte. The next great step in genetics, as I understand it, will be gene therapy. Last year we talked about a genetic disorder called Lesch-Nyhan's syndrome, which leads to retardation and self-mutilation, as a likely candidate for trials at genetic manipulation. Have there been any developments in this area over the past year?

Dr. Goldstein. There have been two significant developments. One is that the actual genes responsible for some neurogenetic disorders have been identified and reproduced and their exact molecular structure is being studied. Secondly, some of these genes are being restructured and tested for amelioration of the disease in naturally occuring animal models of the human condition.

Mr. Conte. In what areas is the most promising work taking place?

Dr. Goldstein. The most promising work on neurological disorders is being done in the area of lysosomal storage diseases, such as Tay-Sachs disease, in which certain substances accumulate in the brain and other tissues because of a specific metabolic defect. The gene for Tay-Sachs disease has been identified and cloned.

Mr. Conte. Isn't Gaucher's disease another genetic disorder that is a candidate for this type of research?

Dr. Goldstein. The NINCDS intramural research program has for many years been involved in the diagnosis of lysosomal storage diseases and study of potential methods for replacement of the defective enzymes which are the basis for such diseases, among which is Gaucher's disease. The gene for regulating the synthesis of the enzyme has been cloned and fundamental studies on how this gene may be inserted into appropriate cells are being actively pursued.

NEUROFIBROMATOSIS

Mr. Conte. What mechanism does NINCDS and these multidisciplinary centers have to compile the various manifestations of neuro-genetic disorders, including neurofibromatosis?

Dr. Goldstein. The most fruitful approach to the study of these diseases is to document the natural history and clinical aspects in a large number of families, over several generations, and identify differences in various manifestations both within and between families. These differences can then be investigated by genetic analysis, using biochemical and linkage methods, to determine if they are due to genetic differences or if they represent clinical variability in expression of the gene. As an example, in neurofibromatosis, the NINCDS has sponsored a working group which will include in its report a documentation of the various manifestations of neurofibromatosis.

Mr. Conte. I understand that the form of NF which affects the central nervous system manifested by bi-lateral acoustic neuroma is also genetic and it has the same pattern of inheritance as the form of NF that affects the peripheral nervous sytem. Does NINCDS have a gene linkage study of the central form of NF?

Dr. Goldstein. The NINCDS has received a grant application proposing to do a gene linkage study of the central form of neurofibromatosis. The application is currently under scientific merit review.

PARKINSON'S DISEASE

Mr. Conte. With regard to the brain, it seems one of the targets of opportunity is now in Parkinson's disease, where a designer drug, MPTP, was found after it ravaged the streets, to mimic the effects of Parkinsonism. Recently, the PBS television show, NOVA, did a very good show on the relationship between MPTP and Parkinson's disease, and seemed to imply that the most likely theory for the cause of Parkinson's disease is environmental, and possibly a class of substances of which Paraquat is a member. Did you have any reaction to that kind of environmental theory?

Dr. Goldstein. While it is clear that Parkinson's disease is not a genetic disorder, the environmental factors contributing to the development of this degenerative disorder remain obscure. Since the description in 1979 of the first patient with MPTP-induced parkinsonism, research at NIH has been active in this area. Because rats are resistant to the toxic effects of MPTP, several years passed before we developed the first animal model of Parkinson's disease by administering this drug to monkeys. Investigators identified MPP$^+$, the toxic metabolite of MPTP, which is a close relative of paraquat. This led to a good deal of speculation that such environmental substances may be involved in the pathogenesis of spontaneous Parkinson's disease. Paraquat, however, because of its chemical nature cannot easily penetrate into the brain and does not itself cause a parkinsonian syndrome -it attacks the lungs and liver. There is at present only fragmentary evidence that any toxin in the environment causes Parkinson's disease and there appear to be important differences between MPTP-parkinsonism and Parkinson's disease.

Mr. Conte. What, in your view, is likely to happen to research in this area now that MPTP is known about?

Dr. Goldstein. The fact that MPTP produces a motor disorder resembling Parkinson's disease only in certain vulnerable species has focused attention on the factors responsible for this vulnerability. If the molecular basis for the vulnerability were better understood, means might be devised to arrest or retard the degenerative process responsible for the progression of Parkinson's disease in man. The animal models make possible exploration of brain tissue implant therapy as well as testing of new drugs which may more effectively control the movement disorder. We have witnessed during the last few years an explosive increase in research in these areas.

Mr. Conte. What opportunities are there in your budget to pursue these leads to the fullest?

Dr. Goldstein. The NINCDS intramural research program has been actively collaborating with investigators in the National Institute of Mental Health to coordinate a multidisciplinary approach to research on the neurological disorders which result from MPTP toxicity. These research efforts will continue and are to be one of the high priority areas for a new NINCDS Laboratory of Neuronal Regeneration and Implantation.

ALZHEIMER'S DISEASE

Mr. Conte. What about Alzheimer's disease, doctor? What have we learned there recently?

Dr. Goldstein. Progress in research in Alzheimer's disease is very encouraging. Progress is being made in understanding the epidemiology of the disease, the mechanism of its development, and the chemistry of the changes that occur. The following are a few of the recent observations made investigators supported by NINCDS.

The largest case-control study of risk factors in Alzheimer's disease has been completed by a team of American and Italian scientists. They have found that: individuals whose brothers and sisters have any form of dementia appear to be 11 times more likely to develop Alzheimer's disease; head trauma and maternal age may be factors which predispose to the disease; and a family history of Down's syndrome, previous thyroid disease, exposure to aluminum, allergies, previous surgical procedures, habits of smoking or drinking wine, or certain personality traits do not seem to be risk factors. Investigators have shown that the incidence of Alzheimer's disease in blacks and whites is similar. Yet another study revealed that in certain families with high rates of Alzheimer's disease, there is evidence of an autosomal dominant pattern of inheritance.

The prion, the putative infectious agent of the animal disease scrapie, has been found to have a proteinaceous composition forming fibers that resemble certain pathological formations in the brains of Alzheimer's patients.

Studies of the chemical pathology that accompanies the neurofibrillary tangles and neuritic plaques characteristic of Alzheimer's disease reveal that two species of proteins, MAP II and tau, present in normal neurons, are highly modified in Alzheimer's disease. The human gene for the tau protein, a component of the tangle, has very recently been identified and cloned. Very recently, it has been reported that the amount of corticotrophin releasing factor (CRF) in the Alzheimer brain is diminished, while receptors for CRF are increased. Thus, new insights into Alzheimer's disease continue to be derived from NINCDS supported research which open possibilities for intervention in the disease.

LEARNING DISABILITIES

Mr. Conte. What activities does the Institute have underway in the area of learning disabilities?

Dr. Goldstein. The Institute has three areas of research underway in learning disabilities. A program announcement was issued to encourage research into brain dysfunction in learning disorders and subsequent awards are currently supporting studies to differentiate among subtypes of the learning handicapped. This type of research will facilitate clinical treatment of the learning handicapped with more appropriate corrective techniques for different groups of children with learning disabilities. Other studies, in response to this program announcement, are investigating the neurochemical abnormalities in attention deficit disorders in children. In addition, a classification of brain disorders of higher function in preschool children is being developed. Preschool children with such disorders often manifest learning disabilities when they reach school age. The classification will permit better design of experimental studies and clinical trials. Finally, an NINCDS award for a multidisciplinary "Center for the Study of the Neurobiological Basis of Language, Learning and Behavior" is investigating developmental disorders of language and spatial cognition, including studies to correlate brain-imaging with electrophysiological data.

SPINE AND BRAIN TRAUMA

Mr. Conte. And in the area of spine and brain trauma, where would you say research is going?

Dr. Goldstein. Current research on spine and brain trauma is aimed at clarifying the cellular and molecular biology associated with mechanisms that control regeneration of damaged nervous tissue. For example, the chemical substances called trophic factors that encourage regeneration are present before birth but not in the adult nervous system. Consequently, investigators are working on isolating these substances, as well as their specific receptors on target nerve cells, and exploring ways to induce their production in adult cells, primarily by learning how to "turn them on and off." In addition, the goal to induce regeneration is being approached by the use of specific nerve cells implanted into the injured brain or spinal cord for the purpose of either producing the substances needed for the remaining tissue to regenerate or replacing the damaged tissue. Thus, some of the most promising research in spine and brain trauma seems to lie in these areas of endeavor: the manipulation of trophic factors and the implantation of neural tissue.

NERVE REGENERATION

Mr. Conte. Are there possibilities for rehabilitation in some of the findings about nerve regeneration and grafting?

Dr. Goldstein. The primary goal of research on nerve regeneration and grafting is to restore, in whole or in part, bodily functions lost as a result of trauma to the central nervous system. Functional restoration, however, depends on highly integrated regeneration. Much more knowledge is needed about the substances that induce neural tissue to replace lost tissue with exactly the same kind of nerve cells which make the same connections as had developed originally and that led to normal function. Only after the capability for normal function has been re-established--a goal now being pursued--can any possibilities for restitution of function be realized, but there will most certainly be many possibilities for rehabilitation of the functionally impaired.

MULTIPLE SCLEROSIS

Mr. Conte. And give us an update, if you would, on the latest developments in research on multiple sclerosis.

Dr. Goldstein. Basic and clinical research on multiple sclerosis is advancing rapidly in a number of areas. The following are some of the most recent observations.

The specific cells involved in the immunologically-mediated destruction in the nervous system of experimental animal models of multiple sclerosis, the conditions which must be present to allow the damage to occur, and the sequence of events in the injury, are being identified with increasing confidence. Highly specific antibodies have now been generated which not only identify the elements of this reaction but which modify and suppress them. Much progress has been made in exploiting these insights in animal models. Parallel studies are being pursued in human multiple sclerosis.

Progress has been made recently in an area called molecular mimicry or homology. Homology is recognized when it can be shown that an infectious agent, viral or bacterial, or components of the agent, bears significant chemical similarity to naturally occurring substances within the host's tissues. As a result of an infection, what was intended to be a beneficial host immune response against the virus or bacterium may instead become a harmful one because the immune system mistakenly attacks the normal host nervous tissue. It appears likely that the response of the immune system to specific infectious agents may lead to chronic and progressive damage to the nervous system in multiple sclerosis. Molecular homology has very recently been demonstrated between a common bacterium of the gastrointestinal tract, *E. coli*, and a component of the brain myelin sheath, MBP, and between the enzyme polymerase of the hepatitis B virus and MBP.

NINCDS scientists have discovered that cells programmed to kill measles virus behave differently in people who have multiple sclerosis than in healthy individuals or people with other disorders. Cells from multiple sclerosis patients kill fewer than normal numbers of cells infected with measles virus. This irregularity may provide an important clue regarding the cause of multiple sclerosis. This demonstrates a specific immune abnormality related to the measles virus that may be at the root of the disease.

For the past several years we have supported clinical trials to explore the value of several agents for the treatment of multiple sclerosis. Active studies are underway on interferon, on treatments which suppress or modulate the immune response, and on drugs of more uncertain mechanisms of action. One promising drug in the latter category, first tested in animal models of multiple sclerosis, is copolymer I. This has been shown to have very promising beneficial effects and few side reactions in a small group of multiple sclerosis patients who showed significant reduction in the frequency of relapses.

CLINICAL TRIALS

Mr. Conte. Are there any clinical trials underway that would be affected by the Gramm-Rudman-Hollings cutback or by the FY 1987 budget request.

Dr. Goldstein. Yes, all of our active clinical trials will have a reduced level of funding as a result of the Gramm-Rudman-Hollings cutback and the FY 1987 budget request.

Mr. Conte. Are there any clinical trials ready to go, that could not get underway due to lack of budgetary resources?

Dr. Goldstein. Yes, there are currently nine new clinical trials that could not be funded in 1987 requiring $14,145,000.

ALZHEIMER'S DISEASE RESEARCH

Mr. Roybal. Although the current research seems to be bringing us closer to understanding the puzzle of Alzheimer's disease, many more questions remain. What are the most significant recent findings?

Dr. Goldstein. Research in Alzheimer's disease is progressing in a very encouraging manner. Progress is being made in understanding the epidemiology of the disease, the mechanism of its development, and the chemistry of the changes that occur. The following are a few of the most significant recent observations made by investigators supported by NINCDS. The largest case-control study of risk factors in Alzheimer's disease has been completed by a team of American and Italian scientists. They have found that: individuals whose brothers and sisters have any form of dementia appear to be 11 times more likely to develop Alzheimer's disease; head trauma and maternal age may be factors which predispose to the disease; and a family history of Down's syndrome, previous thyroid disease, exposure to aluminum, allergies, previous surgical procedures, habits of smoking or drinking wine, or certain personality traits do not seem to be risk factors. Investigators have shown that the incidence of Alzheimer's disease in blacks and whites is similar. Yet another study revealed that in certain families with high rates of Alzheimer's disease, there is evidence of an autosomal dominant pattern of inheritance. The prion, the putative infectious agent of the animal disease scrapie, has been found to have a proteinaceous composition forming fibers that resemble certain pathological formations in the brains of Alzheimer's patients.

Studies of the chemical pathology that accompanies the neurofibrillary tangles and neuritic plaques characteristic of Alzheimer's disease reveal that two species of proteins, MAP II and tau, present in normal neurons, are highly modified in Alzheimer's disease. The human gene for the tau protein, a component of the tangle, has very recently been identified and cloned. Very recently, it has been reported that the amount of corticotrophin releasing factor (CRF) in the Alzheimer brain is diminished, while receptors for CRF are increased. Thus, new insights into Alzheimer's disease continue to be derived from NINCDS-supported research which open possibilities for intervention in the disease.

Mr. Roybal. What, in your opinion, is the next possibility for a breakthrough?

Dr. Goldstein. It is hard to predict the next breakthrough in Alzheimer's disease research. It could be through further progress in any of a number of areas mentioned earlier in which basic and clinical research have provided significant leads. One such possibility for a breakthrough could be in the early diagnosis of Alzheimer's disease. Further development of the most technologically advanced radiological and electrophysical techniques may allow the detection of characteristic changes in brain chemistry and electrical activity which may help diagnose the very early stages of the disease, before serious overt symptoms and signs are evident. Among people over 75, more refined psychometric tests may also serve as a warning sign of the development of the disorder a year or more prior to disabling decline in cognitive functions. It is likely that by employing molecular biological techniques, such as recombinant DNA technology and the production of monoclonal antibodies, a blood test on individuals suspected of having a genetic form of Alzheimer's disease will be developed. The early identification of the disease, by whatever technique, may ultimately permit prevention or therapeutic intervention prior to establishment of irreversible changes.

Mr. Roybal. To what extent will the budget cuts delay our understanding of the etiology of this disease and finding effective treatment and means of prevention?

Dr. Goldstein. Momentum is building up in the neuroscience research community to find the cause, prevention and treatment of Alzheimer's disease because of the encouraging recent progress, the predictable progressively increasing magnitude of the problem, and its social and financial consequences. Progress has been made in understanding the epidemiology, pathology and possible cause of the disease. We expect to continue progress with the resources available to us at this time.

Mr. Roybal. How would additional funds best be spent in this area of research?

Dr. Goldstein. Additional funds could best be spent on basic studies which would allow us to understand the ways in which affected cells in Alzheimer's disease differ from unaffected ones, how and why they die prematurely, and the factors that influence their development and maintenance.

Mr. Roybal. How would that investment advance the process of research?

Dr. Goldstein. The investment in basic research on the nerve cells affected in Alzheimer's disease will bring us closer to an understanding of the mechanisms by which the disease evolves and provide leads to effective intervention in that process.

Mr. Roybal. Briefly describe the clinical research on drug therapy for Alzheimer's disease.

Dr. Goldstein. Clinical research on drug therapy of Alzheimer's disease is based on observations that there are deficiencies of acetylcholine and somatostatin in areas of brain involved in this degenerative disorder. The approaches to therapy are attempts to replace the deficient neurotransmitters by administration of precursors of acetylcholine or of agents which have similar biological effects. The problems of targeting specifically the areas of deficient stimulation without intolerable side effects of excessive stimulation of other regions are currently being addressed. There are also issues of adequately documenting any therapeutic effects which may be obtained in such pilot studies. Advances in assay methods for drugs and in potential therapeutic agents to replace acetylcholine and other neurotransmitters, to prevent unwanted side effects in other regions of the body, and to replace peptides, such as somatostatin, with longer acting substances capable of entering the brain provide hope for the future.

Mr. Roybal. How many patients and intramural staff are involved in those activities during 1986?

Dr. Goldstein. During FY '86 about half a dozen patients with Alzheimer's disease were involved in such pilot studies. There are three physicians and four other NINCDS staff involved in various aspects of these studies.

Mr. Roybal. How many are expected to be involved in 1987?

Dr. Goldstein. We expect to have a similar level of activity in 1987. If particularly promising new findings indicate the requirement for more extensive studies and if the resources are available, additional activity would be initiated.

Mr. Roybal. How does the development of an animal model for Alzheimer's disease enhance the research opportunities for this disease?

Dr. Goldstein. The availability of such a model would allow us to study how and why the disease develops and permit trials of potential therapeutic agents to prevent the development or arrest the progression of the dementia.

Mr. Roybal. Does the current budget proposal allow for adequate development of this research approach?

Dr. Goldstein. Presently, some of the most capable investigators in basic and clinical aspects of Alzheimer's disease are supported by research grants from NINCDS and sister Institutes in their efforts to develop animal models for this disease. The 1987 budget will continue support of these activities.

GRAMM-RUDMAN

Mr. Stokes. Dr. Goldstein, your FY 1986 budget after Gramm-Rudman is $413.024 million. What amount would be required in FY 1987 to maintain this program level?

Dr. Goldstein. In FY 1987, we would need $440,083,000 to maintain a program level based on the FY 1986 Gramm-Rudman cutback.

STROKE

Mr. Stokes. Dr. Goldstein, for several years, we have discussed the incidence of stroke among minorities. Thus, it is not surprising that former Secretary Heckler's task force on black and minority health found that cardiovascular disease and stroke is a major cause of excess deaths among minorities. In fact, stroke deaths among black males are nearly twice as high as among white males. What will you do differently this year in order to respond to the findings of the task force?

Dr. Goldstein. As indicated by the Report of the Secretary's Task Force on Black and Minority Health, stroke deaths among black males occur nearly twice as frequently as among white males. Stroke research investigators are aware of the problem and are actively seeking a better understanding of the specific cause and effect relationships, the pathophysiological processes that lead to such differences, and improved treatment for patients who suffer such debilitating events. The NINCDS plans to continue vigorous research support of these and related important diseases which have a high incidence among minority groups.

Mr. Stokes. Last year, you indicated that two new stroke center applications had been approved for funding. What was the disposition of these applications?

Dr. Goldstein. Two centers have been funded.

Mr. Stokes. Please provide for the record a list of all stroke centers funded in 1985.

Dr. Goldstein. The FY 1985 stroke centers (stroke clinical research centers and stroke clinical program projects) are:

Name of Center	Location
Research Center in Cerebrovascular Disease Cornell University Medical Center	New York, New York
Research Center for Cerebral Vascular Disease University of Miami	Miami, Florida
Duke-V.A. Center for Cerebrovascular Research Duke University	Durham, North Carolina
Cerebrovascular Research Center Wake Forest University	Winston-Salem, NC

Mayo Cerebrovascular Clinical Research Center Mayo Foundation	Rochester, Minnesota
An Interdisciplinary Stroke Program Washington University	St. Louis, Missouri
Cerebrovascular Disease Research Center University of Alabama at Birmingham	Birmingham, Alabama
Interdepartmental Stroke Center Grant Massachusetts General Hospital	Boston, MA
CBF and Metabolism in Stroke and Shock University of Pennsylvania	Philadelphia, PA
Center for Study of Cerebrovascular Disease and Stroke University of Maryland at Baltimore	Baltimore, Maryland
Stroke Clinical Center Grant Oregon Health Sciences University	Portland, Oregon
Prostaglandins in Cerebrovascular Thrombosis Rush-Presbyterian-St. Luke's Medical Center	Chicago, Illinois
Intraventricular Hemorrhage: Pathogenesis and Outcome University of Tennessee Center for Health Sciences	Memphis, Tennessee
Prostaglandins in Cerebrovascular Thrombosis University of Texas Health Science Center	Houston, Texas

Mr. Stokes. How many stroke centers in total will be funded in 1986 and 1987 and in what amounts?

Dr. Goldstein. In 1986, the NINCDS anticipates funding 13 stroke centers for a total of $7,850,000 and, at the level of the 1987 budget, 12 stroke centers for a total of $6,600,000.

BRAIN ARTERY BYPASS SURGERY

Mr. Stokes. The budget justification states that "a major clinical trial to evaluate the efficacy of a commonly performed surgical procedure...has demonstrated that surgery neither improves the outcome of patients with strokes nor prevents additional strokes in stroke prone patients". How important is this finding?

Dr. Goldstein. The extracranial/intracranial (EC/IC) bypass clinical trial demonstrated that surgery neither improves the outcome of patients with stroke nor prevents additional strokes in stroke-prone individuals. This was the first multicentered clinical trial to address a common neurosurgical procedure to determine its efficacy. About 2,000 of these procedures are performed per year at a cost of about $15,000 per patient. Approximately 30 to 40 million dollars have been spent each year in health care costs for this procedure. Because the trial has shown that the procedure is not beneficial, these annual costs may now be avoided. In fact, the investment has already paid for itself, in that half the patients who were entered into the study as eligible for the surgical procedure were, in fact, not operated on. Of even great importance, patients should no longer be subjected to the risks of a surgical procedure which offers no therapeutic advantage to available medical therapy. Finally, this trial has clearly demonstrated that surgical procedures can be subjected to the rigors of controlled, prospective, randomized clinical trials for the development of scientifically valid answers.

Mr. Stokes. What are you doing to put this finding into practice?

Dr. Goldstein. The results of this important clinical trial were first announced at the 8th International Congress of Neurological Surgery in July 1985. Since that time, the results have been widely disseminated and brought to the attention of the medical community at a variety of professional meetings both here and abroad. The definitive paper was published in the New England Journal of Medicine in the Fall of 1985. The public press, news media and television have widely publicized the study and its results. While it is too early for hard data to indicate a decrease in the number of EC/IC bypass operations performed, informal discussions with neurosurgeons have indicated fewer operations are being done. The major impact of the results of this study can be expected to become apparent during the course of this next year.

TRAINING OF MINORITY SCIENTISTS

Mr. Stokes. The budget justification states that "the NINCDS gives special emphasis to the recruitment and research training of clinical investigators in the neurological and communicative disorders. What are you doing to encourage minority scientists to pursue reseach opportunities in these areas?

Dr. Goldstein. The NINCDS will continue to participate in the Academic Research Enhancement Award (AREA) Program, a grant program aimed at improving opportunities for persons in environments not traditionally associated with NIH. This program provides early research experience to students, usually undergraduates, in order to provide an intellectual stimulus toward a research career in the clinical or basic sciences related to neurological and communicative disorders.

Institute staff are actively involved with faculty and students from institutions with longstanding responsibilities to predominantly minority populations to advise them on appropriate NIH mechanisms available for support of research and research training. Several staff have been involved as advisors to the NIH Extramural Associates Program which brings faculty members, and often university Presidents and Chancellors, from minority and women's colleges to NIH for in-depth exposure to the operation of the extramural programs of the various Institutes.

In 1986, NINCDS has committed to continued support of research projects in the neurosciences and communicative sciences within the Minority Biomedical Research Support (MBRS) Program sponsored by the NIH Division of Research Resources. Similarly, the Institute participates in the Minority Access to Research Careers (MARC) Program sponsored by the National Institute of General Medical Sciences.

The NINCDS strongly supports the concept of bringing college students and junior scientists with limited financial means to national meetings of neurological and communicative scientists in order to provide them the opportunity to be involved with the latest scientific advances, and to interact closely with suitable professional mentors. This mechanism, which has been used by NINCDS for several years, has proved particularly attractive to minorities and women.

Mr. Stokes. What is your Institute doing to increase the number of minorities supported through institutional training grants that go to nonminority institutions?

Dr. Goldstein. Although the responsibility for selecting the most appropriate trainees for an institutional training grant resides with the institutional training program director and the applicant institution, NINCDS strongly encourages the priority recruitment of minority members for training appointments. For example, the NINCDS Training Board enthusiastically recommended transfer of National Research Service Award (NRSA) funds to support the postdoctoral research training of a MARC faculty fellow in the laboratory of one of our institutional training grant programs in 1986.

Several revisions in the instructions for preparing Institutional NRSA applications are being made in 1986. More detail will be required in describing the qualifications of prospective trainees, criteria and procedures by which trainees will be selected and steps to be taken in recruiting individuals from minority groups. Competing continuation applications for ongoing research training programs will also include cumulative statistics concerning subsequent career development of minority and non-minority trainees.

HISTORICALLY BLACK COLLEGES

Mr. Stokes. In 1984, the NINCDS awarded a very small amount, $251,886 to historically black colleges. What are the comparable figures for 1985?

Dr. Goldstein. The Institute awarded $123,561 to Historically Black Colleges in 1985.

Mr. Stokes. What are your goals for 1986 and 1987?

Dr. Goldstein. It is anticipated that this grant will be submitted as a competing renewal application in 1987 and we are unable to estimate the cost at this time.

MINORITY PROGRAM AND PERSONNEL ISSUES

Mr. Stokes. Dr. Goldstein, do you establish goals for your senior administrators for addressing minority program and personnel issues?

Dr. Goldstein. The Institute annually prepares a Federal Equal Opportunity Recruitment Plan (FEORP) which identifies job series where there is underrepresentation by women and minorities and establishes goals for broadening candidate selection pools to include more women and minority candidates. These plans are widely disseminated among senior managers. Periodic reports are made at senior staff meetings on these plans and progress in recruitment of women and minorities. The Institute sponsors an annual All Employees Meeting which provides information to both the professional staff and support staff on personnel and equal employment opportunity issues, problems and plans. Senior managers are required to incorporate efforts for recruitment of women and minorities in their hiring plans.

Mr. Stokes. If not, why not?

Dr. Goldstein. Senior managers are required to address the requirements of the Institute's Federal Equal Opportunity Recruitment Plan.

Mr. Stokes. How do you hold your senior officers accountable for meeting those goals?

Dr. Goldstein. The annual performance work plan for each senior manager includes a work element requiring each individual to apply equal opportunity principles in recruitment, training promotion and awards. Managers' performance on this element is evaluated each year by higher level supervisors and performance reviewers.

Mr. Stokes. For the record, please supply the following information for SES positions, senior level administrative positions, and senior level professional positions in your Institute. The current number of all such positions and the current number of these positions occupied by blacks.

Dr. Goldstein. The following table reflects these data:

	Total Number	Number of Blacks
SES	18	0
Senior Level Administrative	15	5
Senior Level Scientific	44	1

AIDS

Mr. Stokes. What is the significance of the fact that 40 percent of AIDS patients develop brain lesions which contain the AIDS virus?

Dr. Goldstein. This means that something special exists, either in the virus, in the brain itself, or in the way the virus and brain interact. A significant number of patients manifest neuro-behavioral changes due to brain involvement prior to or without ever showing evidence of AIDS elsewhere in the body. We do not understand the reason for the predilection of the virus for the nervous system. This should be investigated intensively because an understanding of this phenomenon may provide significant information about the nature of the virus and provide leads regarding prevention or cure of the disease.

Mr. Stokes. Can you tell us more about AIDS dementia, the mental deterioration associated with advanced AIDS, and what proportion of AIDS victims suffer from it?

Dr. Goldstein. AIDS dementia is a progressive disorder of the brains of children and adults characterized by cognitive, motor and behavioral disturbances. Of these, cognitive dysfunction is most common. Symptoms begin with difficulty in concentration and impaired memory and progress in some to mutism and incapacity for all but the most rudimentary personal and social interactions. Early motor disturbances include tremor of the hands and instability in walking, and eventually paralysis with urinary and bowel incontinence. Social withdrawal and apathy are common. A minority of patients develop an organic psychosis with paranoia and hallucinations. Pathologically, the disease affects predominantly the cerebral white matter and deep gray structures.

As many as sixty-five percent of AIDS patients had AIDS dementia in a recent autopsy-proven series. Children with AIDS may be even more commonly affected.

EPILEPSY RESEARCH

Mr. Stokes. What type of research on epilepsy are you supporting at the present time?

Dr. Goldstein. Studies include research on the basic processes responsible for generation, spread, and control of seizures, as well as aspects of cerebral metabolism, nervous system maturation, genetics and neuroendocrinology relevant to epilepsy. Other investigators are examining the mechanisms of action, metabolism and adverse effects of antiepileptic drugs and are conducting clinical studies of epilepsy, including neuroimaging, surgical therapy for epilepsy, and clinical trials for the prevention of epilepsy. A small number of grants support the development of new technologies such as computerized electroencephalography and magnetoencephalography. The Antiepileptic Drug Development (ADD) Program is a contract supported effort to develop more effective and less toxic drugs for epilepsy. The ADD Program encompasses all elements of drug development from identification of potentially useful therapeutic agents through controlled efficacy trials. The Institute has also supported over the years a number of symposia related to epilepsy.

Mr. Stokes. How many epilepsy research centers are there?

Dr. Goldstein. Currently, there are ten epilepsy research centers and program projects compared to nine in FY 1985.

Mr. Stokes. What are the funding allocations for these centers in 1985, 1986 and 1987?

Dr. Goldstein. In 1985, the nine centers were awarded $6,771,000. In 1986, three of these need to compete for renewal and if all three are successful, the funding estimates would be $7,500,000 in 1986 and $6,900,000 in 1987 for these ten centers.

Mr. Stokes. What are you doing to stimulate the number of investigators involved in clinical research on epilepsy?

Dr. Goldstein. The Institute stimulates the number of investigators involved in clinical research in epilepsy in three ways. First, a special research award, the Clinical Investigator Development Award, provides salary and research support to young investigators interested in epilepsy as well as other areas of clinical neurological research. Second, the Institute supports epilepsy workshops for young investigators held in conjunction with national meetings of professional societies to permit interaction of young investigators with established epileptologists. And finally, the Institute issues announcements specifically soliciting research in areas of clinical epilepsy.

DOWNWARD NEGOTIATIONS

Mr. Early. In your professional judgment, Doctor, do you have any serious concerns about the size of the downward negotiations the project grants are being forced to take under this budget request?

Dr. Goldstein. These reductions could mean delays or modifications of the research proposed. Proposals will be carefully reviewed to minimize any adverse effect on the research being done.

Mr. Early. The budget indicates that direct costs for research centers will be reduced by 4% in FY 86 and 14% in FY 87. Are reductions of this size something we need to be concerned about?

Dr. Goldstein. We are concerned and will make very effort to minimize the effect such reductions will have. However, some investigators may need to rethink planned approaches and/or delay some experiments in order to stay within the amount awarded.

Mr. Early. What effect will these cuts have on the research programs at these centers?

Dr. Goldstein. We hope to minimize adverse effects on research quality. We anticipate that the primary effect would be to slow the pace of research and in some cases delay certain experiments requiring specialized personnel and equipment.

Mr. Early. How will the reduction in the size and scope of the centers program affect NINCDS program plans--both immediate and long range?

Dr. Goldstein. NINCDS science administrators will work closely with research centers directors to try to minimize the immediate impact. In the longer term, we will need to consider limiting more severely the scope of issues to be given priority for center funding. Scientific excellence and research opportunities will continue to be the guiding principles.

RESEARCH CENTERS

Mr. Early. I understand that 38 research centers are to be supported in FY 86 and in FY 87. How many centers are up for renewal in FY 86?

Dr. Goldstein. There are eight centers which must compete for renewal in FY 1986.

Mr. Early. For the record provide the names and locations of these centers.

Dr. Goldstein. The following is a list of those centers:

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

1986 COMPETING RESEARCH CENTERS

Principal Investigator, Institution Location, Project Title

Toole, James F.
Wake Forest University
Winston-Salem, North Carolina
Cerebrovascular Research Center

Whisnant, Jack P.
Mayo Foundation
Rochester, Minnesota
Cerebrovascular Clinical Research Center

Barchi, Robert L./Pleasure, David E.
University of Pennsylvania
Philadelphia, Pennsylvania
Studies of Neuromuscular Diseases

Halsey, James H., Jr.
University of Alabama in Birmingham
Birmingham, Alabama
Cerebrovascular Disease Research Center

Weiner, Norman
University of Colorado Health Sciences Center
Denver, Colorado
Basal Ganglia Disorders and Neurotransmitter Function

Yahr, Melvin D.
Mount Sinai School of Medicine
New York, New York
Clinical Center for Research in Parkinson's

Prince, David A.
Stanford University
Stanford, California
Epilepsy Research Program

Gumnit, Robert J.
University of Minnesota of Minneapolis-Saint Paul
Minneapolis, Minnesota
Minnesota Comprehensive Epilepsy Program

Mr. Early. How many centers will be up for renewal in FY 87?

Dr. Goldstein. Twelve centers must compete for renewal in FY 1987.

Mr. Early. Provide the names and locations of these for the record.

Dr. Goldstein. The following is a list of those centers:

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

1987 COMPETING RESEARCH CENTERS

Principal Investigator, Institution Location, Project Title

Glaser, Gilbert H./Mattson, Richard H.
Yale University
New Haven, Connecticut
Neurological Research Center (Epilepsy)

Davis, James N.
Duke University
Durham, North Carolina
Duke-V.A. Center for Cerebrovascular Research

Hunt, William E.
Ohio State University
Columbus, Ohio
Spinal Cord Injury Research Center

Collins, William F., Jr.
Yale University
New Haven, Connecticut
A Center for Acute Spinal Cord Injury

Koprowski, Hilary
Wistar Institute of Anatomy and Biology
Philadelphia, Pennsylvania
Etiology and Pathogenesis of Multiple Sclerosi

Kellaway, Peter A.
Baylor College of Medicine
Houston, Texas
Epilepsy Research Center

Bartfeld, Harry
St. Vincent's Hospital and Medical Center of New York
New York, New York
Cause and Mechanisms of Amyotrophic Lateral Sclerosis

Giebink, G. Scott
University of Minnesota of Minneapolis-Saint Paul
Minneapolis, Minnesota
Pathogenesis of Otitis Media

Fields, Bernard N.
Harvard University
Boston, Massachusetts
The Molecular Basis of Viral Injury to the Nervous System

Netsell, Ronald
Father Flanagan's Boys' Home
Boys Town, Nebraska
Communicative Disorders in Children

Johnson, Kenneth P.
University of Maryland
Baltimore, Maryland
Amyotrophic Lateral Sclerosis and Multiple Sclerosis Clinical Center Grant

Price, Donald L.
Johns Hopkins University School of Medicine
Baltimore, Maryland
The Forebrain Cholinergic System in Health and Disease(Alzheimer's)

JAVITS CENTERS

Mr. Early. Provide a list of the Jacob Javits Neuroscience Center award recipients, and indicate the size of each award.

Dr. Goldstein. The Jacob Javits Neuroscience Center Award recipients and total costs awarded in Fiscal Year 1985 were: University of California, San Francisco (Dr. Stanley B. Prusiner), $952,000; Rockefeller University (Dr. Gerald M. Edelman), $1,120,000; Yale University (Dr. Pasco Rakic), $1,102,000; and Washington University, St. Louis (Dr. Gerald D. Fischbach), $975,000. Non-competing continuations to be awarded later in Fiscal Year 1986 are currently estimated to be $918,000 to the University of California; $1,056,000 to Rockefeller; $955,000 to Yale; and $843,000 to Washington University.

Mr. Early. What would these awards be under the FY 87 request?

Dr. Goldstein. We estimate that the awards scheduled for September 1987 will be approximately $856,000 to California, $979,000 to Rockefeller, $930,000 to Yale, and $708,000 to Washington University.

Mr. Early. Are there any high priority clinical trials which are ready but cannot be initiated because of lack of funds in the FY 87 request?

Dr. Goldstein. Yes, there are currently nine new clinical trials that could not be funded in 1987.

Mr. Early. If so please provide a list of these, along with a brief description and the associated costs, incuding first year costs.

Dr. Goldstein. The following new clinical trials could not be initiated in 1987. The total 1987 estimate for these trials is $14,145,000.

> Stroke prevention by surgical carotid endarterectomy in asymptomatic patients - FY 1987 estimate: $3,019,000; total estimate: $27,394,000 for 8 years.
>
> This is a clinical trial to study the efficacy of medical versus surgical therapy to prevent stroke in

asymptomatic patients with stenosis (narrowing) of the distal common and/or internal carotid artery.

Stroke prevention by surgical carotid endarterectomy in symptomatic patients - FY 1987 estimate: $4,176,000; total estimate: $29,177,000 for 8 years.

This is a clinical trial similar to the one above for the study of the same procedure in symptomatic patients.

Study of Cyclosporin A in the management of autoimmune disorders - FY 1987 estimate: $500,000; total estimate: $1,575,000.

This clinical trial will study the effects of Cyclosporin A, a powerful immunosuppressor, on the management of autoimmune disorders such as multiple sclerosis, myasthenia gravis, and Guillian-Barre syndrome.

Study of monoclonal antibody for the treatment of multiple sclerosis - FY 1987 estimate: $500,000; total estimate: $1,575,000.

Monoclonal antibodies (MAbs) are emerging as a promising vehicle to modulate antigenic expression and immunological response. MAbs against T cells will be employed in an effort to prevent progression of multiple sclerosis.

Study of monoamine oxidase (MAO) inhibitors for the treatment of Parkinson's disease - FY 1987 estimate: $2,000,000; total estimate: $7,0[illegible],000.

MAO inhibitors may provide a new approach to the prevention of the neuronal cell degeneration induced by the toxin MPTP. This clincal trial will study the use of MAO inhibitors in Parkinson's disease.

Study of orphan products for the treatment of rare movement disorders such as Tourette's syndrome - FY 1987 estimate: $1,200,000; total estimate: $3,600,000.

A clinical trial on the use of an orphan drug product for the treatment of rare movement disorders such as Tourette's syndrome.

Study of Copolymer 1 in the treatment of multiple sclerosis - FY 1987 estimate: $2,250,000; total estimate: $6,750,000.

A clinical trial on the use of a synthetic peptide, Copolymer 1 in the treatment of exacerbating-remitting multiple sclerosis. A pilot study has already indicated the potential usefullness of this new material.

Two separate new studies of the efficacy of new antiepileptic drugs in patients with complex partial seizures - FY 1987 estimate: $500,000; total estimate: $1,500,000, a type of epilepsy.

These clinical trials will study the efficacy of promising new antiepileptic drugs in patients with complex partial seizures, a type of epilepsy.

SMALL BUSINESS INNOVATIVE RESEARCH PROGRAM

Mr. Early. Doctor, briefly would you tell us how your Institute is using the Small Business Innovative Research program?

Dr. Goldstein. The NINCDS employs both grant and contract mechanisms in meeting the goals of the SBIR program. The NINCDS program focusses primarily on applied research in the areas of hearing loss, nerve stimulator, diagnostic procedures and clinical therapy.

Mr. Early. Then for the record provide a bit more detail?

Dr. Goldstein. The NINCDS encourages SBIR grant applications aimed at improved diagnosis, treatment, and prevention of disorders of the nervous system, the neuromuscular apparatus, the ear, human communication and the special senses of taste, smell, touch and pain. Examples of grant funded research include studies examining the possibility of providing: an improved hearing screening device, a genetic linkage test for Huntington's disease, a therapy device for head trauma, and a computerized test for dyslexia. The Institute utilizes the grant mechanism as its primary instrument in the SBIR program; approximately 80% of the set-aside in 1986 was used to support investigator initiated grant applications.

In addition, the NINCDS has solicited specific contract proposals in five areas: multipoint tactile array stimulation for the profoundly deaf, instrumentation and software to measure and analyze certain chemicals of significance in the central nervous system, new approaches to data management in neurodiagnostic monitoring, development and propagation of animal models of neurological diseases, and a device to block reversibly the action of certain peripheral nerves which limits the usefulness of some neural prostheses.

PARKINSON'S DISEASE

Mr. Early. For the record insert a list which compares your total budget and the amounts available for Parkinson's Disease research for FY 85, the FY 86 post-sequestration level (without the rescission), and the FY 87 estimates.

Dr. Goldstein. The following table compares Parkinson's disease related research with the total NINCDS budget.

	Total NINCDS Budget	Parkinson's Disease
1985	$393,978,000	$18,566,000
1986	$413,292,000	$19,436,000
1987	$399,351,000	$18,787,000

Mr. Early. If an increase over the FY 87 request is provided, how would you use these additional funds?

Dr. Goldstein. The intramural research program would use additional funds appropriated for Parkinson's disease research to further develop the program of the new Laboratory of Regeneration and Neuronal Implantation. Studies which seek methods to replace the neurotransmitter deficits in the experimental animal model for Parkinson's disease would be accelerated. Funds would also be used to enhance studies of PET imaging to study both humans and animals with MPTP-induced parkinsonism. For extramural programs, additional funds would be used to support meritorious basic investigations on the etiology and pathogenesis of Parkinson's disease and for clinical trials using innovative approaches based upon recent significant observations. Based on the MPTP model for Parkinson's, a clinical trial of new therapies directed at retarding the progression of early parkinsonism has been proposed. Additional funds would be used to pursue these exciting leads.

Additional support would be provided for basic studies which would allow an understanding of the ways in which affected cells in Parkinson's disease differ from unaffected ones, how and why they die prematurely, and the factors that regulate their development and maintenance.

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed by lack of funds in the FY 87 budget?

Dr. Goldstein. A number of meritorious extramural proposals to study the MPTP-induced selective neuronal cell destruction and the functional response to fetal brain tissue implantation as these relate to the etiology, pathogenesis and possible treatment of Parkinson's disease could not be supported. Moreover, the newly proposed clinical trial of prevention of progression would not be funded. Expanded use of the MPTP model would be delayed in the intramural research program.

Mr. Early. Please provide for the record a list of these, along with a brief description and the funding requirements associated with each.

Dr. Goldstein. The following is a list of new research opportunities which would be lost due to lack of funds in the FY 87 budget.

Basic studies on MPTP: $2,000,000.

Opportunities have been opened for innovative research into the pathogenesis and treatment of Parkinson's disease as a result of the identification of MPTP-induced models of Parkinson's disease in primates and other animals. There has been an increase in the number of new applications to study these models.

Studies on neural tissue implantation: $2,000,000.

Fetal neural tissue implantation has been employed very recently and successfully to study the growth and development and regeneration in experiemntal animals models of various human neurological disorders, especially Parkinson's disease. The potential for a favorable clinical effect of tissue implantation in patients with Parkinson's disease motivated foreign scientists to implant adrenal medullary tissue into four patients, with, as yet, indeterminate results. The FY 1987 budget will delay the fundamental studies in pr~~imate~~s which need to be done before any such effort is initiated in the United States.

Studies on selective vulnerability: $2,000,000.

New basic studies which will lead to an understanding of the ways in which the affected nerve cells in Parkinson's disease differ from unaffected ones, how and why they die prematurely, and the factors that regulate their development and maintenance would be delayed or eliminated in the FY 87 budget.

Multi-Institutional Trial of Anti-Oxidative Pharmacotherapy for Parkinson's Disease: $2,000,000.

Supported by recent basic findings using the compound MPTP it has been proposed that chronic anti-oxidant therapy will delay or prevent the progressive and selective degeneration of the substantia nigra and the clinical decline of patients with Parkinson's disease. A proposal for a three year controlled prospective evaluation of therapy which we anticipate receiving in FY 1987 would not be supported if funds were lacking from the FY 1987 budget.

Mr. Early. Doctor, will any significant research initiative currently underway be halted or seriously delayed due to FY 87 funding levels?

Dr. Goldstein. The highest priority research initiatives will continue to be supported in order to provide the base for the most important aspects of research on Parkinson's disease.

Mr. Early. To what extent will there be major reductions in the scope of ongoing or new initiatives because of the FY 87 funding levels?

Dr. Goldstein. Ongoing and new research will likely be stretched out or delayed because of the downward negotiations.

Dr. Early. For the record, provide a list of these along with a brief description and the amounts associated with each initiative.

Dr. Goldstein. Support would be provided but ongoing and new research grants will have to be negotiated downward. In 1987, an additional $2,350,000 would be needed to maintain the 1986 appropriation level of research on Parkinson's disease.

CONTRACT FUNDING

Mr. Hoyer. In fiscal 1985, your Institute spend $14.2 million on project contracts. This amount is estimated to drop by 12% to $12.5 million during the current fiscal year and to $11.5 million during fiscal 1987 - 19% less that the amount available during 1985. What areas of research will be most affected by this reduced level of funding?

Dr. Goldstein. Research areas which will be most affected include the drug development program for epilepsy and low incidence--rare--diseases, the neural prosthesis program, animal models and drug evaluations in stroke and nervous system trauma, slow virus studies, and research on disorders of hearing and speech.

EPILEPSY RESEARCH

Mr. Hoyer. What about epilepsy?

Dr. Goldstein. Epilepsy contracts were $2,267,000 in 1985 and are estimated at $2,007,000 in 1986 and $1,845,000 in 1987.

Mr. Hoyer. Would you provide the Subcommittee with a breakdown of the Institute's contract funding by area of research for each fiscal year from 1984 through your fiscal 1987 estimates?

Dr. Goldstein. The following table provides a breakdown by area of research:

1984 - 1987 Research and Development Contracts
by Research Activity
(in thousands of dollars)

Research Activity	1984	1985	1986 Estimate	1987 Estimate
Neurological disorders of early life	$ 976	$ 536	$ 475	$ 436
Neurological disorders of adult life	662	250	221	204
Stroke	2,207	2,556	2,263	2,081
Epilepsy	3,429	2,267	2,007	1,845
Demyelinating disorders	517	256	227	208
Neuromuscular disorders	322	69	61	56
Infectious diseases of the nervous system	907	1,044	924	850
Trauma and injury	1,449	861	762	701
Nervous system function	22	334	295	273
Hearing and equilibrium	439	1,015	899	826
Speech and language	993	1,090	965	887
Neural prosthesis	3,281	3,885	3,440	3,162
TOTAL, R&D contracts	15,204	14,163	12,539	11,529

RESEARCH CENTERS

Mr. Hoyer. The Justification Document states that 38 Research Centers were supported by your Institute during fiscal 1985 and the same number will be supported this year and again during fiscal 1987. Would you please provide a list of the research centers that will be up for renewal during fiscal 1987?

Dr. Goldstein. The following research centers must compete for renewal in 1987:

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

1987 COMPETING RESEARCH CENTERS

Principal Investigator, Institution Location, Project Title

Glaser, Gilbert H./Mattson, Richard H.
Yale University
New Haven, Connecticut
Neurological Research Center (Epilepsy)

Davis, James N.
Duke University
Durham, North Carolina
Duke-V.A. Center for Cerebrovascular Research

Hunt, William E.
Ohio State University
Columbus, Ohio
Spinal Cord Injury Research Center

Collins, William F., Jr.
Yale University
New Haven, Connecticut
A Center for Acute Spinal Cord Injury

Koprowski, Hilary
Wistar Institute of Anatomy and Biology
Philadelphia, Pennsylvania
Etiology and Pathogenesis of Multiple Sclerosis

Kellaway, Peter A.
Baylor College of Medicine
Houston, Texas
Epilepsy Research Center

Bartfeld, Harry
St. Vincent's Hospital and Medical Center of New York
New York, New York
Cause and Mechanisms of Amyotrophic Lateral Sclerosis

Giebink, G. Scott
University of Minnesota of Minneapolis-Saint Paul
Minneapolis, Minnesota
Pathogenesis of Otitis Media

Fields, Bernard N.
Harvard University
Boston, Massachusetts
The Molecular Basis of Viral Injury to the Nervous System

Netsell, Ronald
Father Flanagan's Boys' Home
Boys Town, Nebraska
Communicative Disorders in Children

Johnson, Kenneth P.
University of Maryland
Baltimore, Maryland
Amyotrophic Lateral Sclerosis and Multiple Sclerosis Clinical Center Grant

Price, Donald L.
Johns Hopkins University School of Medicine
Baltimore, Maryland
The Forebrain Cholinergic System in Health and Disease(Alzheimer's)

Mr. Hoyer. Would you provide a description of each of the centers supported last year as well as those currently being supported?

Dr. Goldstein. The following is a list of research centers.

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

RESEARCH CENTERS 1985 - 1987

Principal Investigator, Institution Location, Project Title

Plum, Fred
Cornell University Medical Center
New York, New York
Research Center in Cerebrovascular Disease
Competing in 1989

Ginsberg, Myron D.
University of Miami
Miami, Florida
Research Center for Cerebral Vascular Disease
Competing in 1990

Glaser, Gilbert H./Mattson, Richard H.
Yale University
New Haven, Connecticut
Neurological Research Center(Epilepsy)
Competing in 1987

Davis, James N.
Duke University
Durham, North Carolina
Duke-V.A. Center for Cerebrovascular Research
Competing in 1987

Toole, James F.
Wake Forest University
Winston-Salem, North Carolina
Cerebrovascular Research Center
Competing in 1986

Whisnant, Jack P.
Mayo Foundation
Rochester, Minnesota
Cerebrovascular Clinical Research Center
Competing in 1986

Raichle, Marcus E.
Washington University
Saint Louis, Missouri
An Interdisciplinary Stroke Program
Competing in 1990

Barchi, Robert L./Pleasure, David E.
University of Pennsylvania
Philadelphia, Pennsylvania
Studies of Neuromuscular Diseases
Competing in 1986

Halsey, James H., Jr.
University of Alabama in Birmingham
Birmingham, Alabama
Cerebrovascular Disease Research Center
Competing in 1986

Weiner, Norman
University of Colorado Health Sciences Center
Denver, Colorado
Basal Ganglia Disorders and Neurotransmitter Function
Competing in 1986

Ward, Paul H.
University of California at Los Angeles
Los Angeles, California
Communicative Disorders Clinical Research Center
Competing in 1988

Flamm, Eugene S.
New York University
New York, New York
Clinical Research Center for Acute Spinal Cord Injuries
Competing in 1988

Hunt, William E.
Ohio State University
Columbus, Ohio
Spinal Cord Injury Research Center
Competing in 1987

Collins, William F., Jr.
Yale University
New Haven, Connecticut
A Center for Acute Spinal Cord Injury
Competing in 1987

Zervas, Nicholas T.
Massachusetts General Hospital
Boston, Massachusetts
An Interdepartmental Stroke Research Program
Competing in 1988

Reivich, Martin
University of Pennsylvania
Philadelphia, Pennsylvania
Cerebral Blood Flow and Metabolism in Stroke and Shock
Competing in 1990

Koprowski, Hilary
Wistar Institute of Anatomy and Biology
Philadelphia, Pennsylvania
Etiology and Pathogenesis of Multiple Sclerosis
Competing 1987

Kellaway, Peter A.
Baylor College of Medicine
Houston, Texas
Epilepsy Research Center
Competing in 1987

Bartfeld, Harry
St. Vincent's Hospital and Medical Center of New York
New York, New York
Cause and Mechanisms of Amyotrophic Lateral Sclerosis
Competing in 1987

Yahr, Melvin D.
Mount Sinai School of Medicine
New York, New York
Clinical Center for Research in Parkinson's
Competing in 1986

Bornstein, Murray B.
Yeshiva University
New York, New York
Pathogenesis and Treatment of Multiple Sclerosis
Competing in 1989

Duvall, Arndt J., III
University of Minnesota of Minneapolis-Saint Paul
Minneapolis, Minnesota
Mechanisms of Auditory and Vestibular Dysfunction
Competing in 1988

Prince, David A.
Stanford University
Stanford, California
Epilepsy Research Program
Competing in 1986

Oldstone, Michael B.
Scripps Clinic and Research Foundation
La Jolla, California
Multiple and Amyotrophic Lateral Sclerosis Pathogenesis
Competing in 1990

Young, Harold F./Becker, Donald P.
Virginia Commonwealth University
Richmond, Virginia
Head Injury Clinical and Laboratory Research Center
Competing in 1989

Giebink, G. Scott
University of Minnesota of Minneapolis-Saint Paul
Minneapolis, Minnesota
Pathogenesis of Otitis Media
Competing in 1987

Ferrendelli, James A.
Washington University
Saint Louis, Missouri
Basic Mechanisms of Seizures
Competing in 1990

Gumnit, Robert J.
University of Minnesota of Minneapolis-Saint Paul
Minneapolis, Minnesota
Minnesota Comprehensive Epilepsy Program
Competing in 1986

Price, Thomas R.
University of Maryland at Baltimore
Baltimore, Maryland
Clinical Stroke Research Center
Competing in 1990

Abbs, James H.
University of Wisconsin at Madison
Madison, Wisconsin
Speech Movement Research With an X-Ray Microbeam
Competing in 1990

Fields, Bernard N.
Harvard University
Boston, Massachusetts
The Molecular Basis of Viral Injury to the Nervous System
Competing in 1987

Ward, Arthur A., Jr.
University of Washington
Seattle, Washington
Center for Clinical Research in Epilepsy
Competing in 1990

Kare, Morley R.
Monell Chemical Senses Center
Philadelphia, Pennsylvania
Chemosensory Clinical Research Center
Competing in 1989

Hummeler, Klaus/Watkins, John B.
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania
Pathogenesis of Reye's Syndrome
Competing in 1988

Netsell, Ronald
Father Flanagan's Boys' Home
Boys Town, Nebraska
Communicative Disorders in Children
Competing in 1987

Johnson, Kenneth P.
University of Maryland at Baltimore
Baltimore, Maryland
Amyotrophic Lateral Sclerosis and Multiple Sclerosis
Clinical Center Grant
Competing in 1987

Bigner, Darrell D.
Duke University
Durham, North Carolina
Malignant Human Gliomas and Medulloblastoma
Competing in 1989

Price, Donald L.
Johns Hopkins University
Baltimore, Maryland
The Forebrain Cholinergic System in Health and Disease
Competing in 1987

Bada, Henrietta S.
University of Tenn Center Health Science
Memphis, Tennessee
Intraventrical Hemorrhage: Pathogenesis and Outcome
Competing in 1988

Johnson, Richard T.
Johns Hopkins University
Baltimore, Maryland
Demyelinating Diseases of the Nervous System
Competing in 1990

Yost, William A.
Loyola University of Chicago
Chicago, Illinois
Information Processing by the Auditory System
Competing in 1988

Tallal, Paula
University of California San Diego
Center for the Study of the Neurological Basis of Language
Competing in 1990

Wu, Kenneth K.
Rush University
Chicago, Illinois
Prostaglandins in Cerebrovascular Thrombosis
Competing in 1988

EPILEPSY RESEARCH

Mr. Hoyer. How many of the existing centers specialize in epilepsy research?

Dr. Goldstein. There are 6 Research Centers and 3 clinical program projects, a total of 9 large centers which specialize in epilepsy research.

INTRAMURAL RESEARCH

Mr. Hoyer. The Justification document indicates that the intramural research program will be reduced $520,000 during fiscal year 1987 through "decreases in lower priority (research) areas." Specifically what research will be affected by this reduction?

Dr. Goldstein. The reduction in expenditures of the NINCDS, intramural reseach program will reflect the completion of perinatal studies involving use of primates to examine infectivity of certain viruses, a reduction in research on the biochemical basis of the conditioned reflex and redirection of efforts in genetic disorders.

DIABETES RESEARCH

Mr. Porter. In FY 1984, diabetes funding as a portion of the budget for the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) was $7.4 million. In FY 1985, this figure dropped by almost 50% to $4.3 million. NINCDS has also recently dropped out of the Diabetes Control and Complications Trial (DCCT) which is a massive effort to gauge the impact of strict control of blood sugar levels to prevent diabetes complications. Dr. Goldstein, why have the Institute's priorities changed so abruptly in regard to diabetes research?

Dr. Goldstein. The Institute has not changed its priorities. Institute reports of diabetes related research are based upon a continual review of ongoing as well as new research in the neurological sciences to assess the current relevance to diabetes. Changes in scientific emphasis by the investigators themselves, rather than any change in Institute priorities, result in fluctuations in the funds awarded in diabetes related research, as it does in other research areas.

Mr. Porter. Why did the Institute drop out of the DCCT?

Dr. Goldstein. In FY 1983, after review of scientific merit by an extramural committee of research experts and upon recommendation of the NINCDS National Council, the Institute participated in the feasibility phase of the Diabetes Control and Complications Trial (DCCT). In FY 1986, a committee of experts reviewed the results of the feasibility study and concluded that the technology available for assessment of neurological function was not sufficient to answer the questions asked in the NINCDS funded portion of the trial. Consequently, the Council recommended no further Institute support for the neurological aspects of the trial.

Mr. Porter. I would appreciate your providing me with a detailed list of the continuing diabetes-related research projects sponsored by the Institute. Could you also indicate the timing for these projects.

Dr. Goldstein. The following is a list of diabetes-related projects supported by the NINCDS.

DIABETES RESEARCH

Principal Investigator, Institution Location, Project Title

Greer, William
Gulf South Research Institute
Baton Rouge, Louisiana
Supporting Services on Viral Research Project
Project ends in 1986

Jakinovich, William
Herbert H. Lehman College
Bronx, New York
Specificy of Sweet Taste Response
Project ends in 1986

Dichiro, Giovanni
NINCDS, NIH
Bethesa, Maryland
Positron Emission Tomography
Project ends in 1989

Fishman, Peter H.
NINCDS, NIH
Biosynthesis and Function of Glycosphingolipids, and Other Glycoconjugates
Bethesda, Maryland
Project ends in 1989

Grady, Patricia
University of Maryland at Baltimore
Baltimore, Maryland
Center for Cerebrovascular Disease and Stroke
Project ends in 1990

Passonneau, Janet V.
NINCDS, NIH
Bethesda, Maryland
Metabolic Profiles in Normal and Diseases Retina
Project ends in 1986

Plum, Fred
Cornell University Medical Center
New York, New York
Research Center in Cerebrovascular Disease
Project ends in 1989

Schoenberg, Bruce S.
NINCDS, NIH
Bethesda, Maryland
Epidemiology of Cerebrovascular Diseae in Adults
Project ends in 1992

Fisher, Mark J.
University of Southern California
Los Angeles, California
Hemorheological Factors in Cerebral Ischemia
Project Ends in 1987

McGee, Richard, Jr.
Georgetown University
Washington, D. C.
Role of Membrane Lipids in Controlling Cellular Function
Project ends in 1987

Gajdusek, D. C.
NINCDS, NIH
Bethesda, Maryland
Chronic CNS Disease Studies - Slow, Latent and Temperate Virus Infections
Project ends in 1992

Gajdusek, D. C.
NINCDS, NIH
Bethesda, Maryland
Neurobiology - Child Development, and Disease Patterns in Primitive Culture
Project ends in 1989

Powell, Henry C.
University of California at San Diego
La Jolla, California
Pathogenesis of Toxic and Metabolic Neuropathies
Project ends in 1986

Quarles, Richard H.
NINCDS, NIH
Bethesda, Maryland
Glycoprotein of Myelin in Development and Disease
Project ends in 1986

Schoenberg, Bruce S.
NINCDS, NIH
Bethesda, Maryland
Reviews of Epidemiologic Aspects of Neurologic Disease
Project ends in 1992

Wolf, Philip A.
Boston University
Boston, Massachusetts
Precursors of Stroke Incidence and Prognosis
Project ends in 1986

Latov, Norman
Columbia University
New York, New York
Mechanisms in Human Peripheral Neuropathies
Project ends in 1988

Hoffert, Marvin J.
University of Wisconsin
Madison, Wisconsin
Studies of Peripheral Nerve Physiology and Pharmacology
Project ends in 1970

Pelligrino, Dale A.
Michael Reese Hospital
Chicago, Illinois
Diabetes, Insulin, and Brain Matabolism
Project ends in 1987

Windebank, Anthony J.
Mayo Foundation
Rochester, Minnesota
Cellular Mechanisms of Experimental Lead Neuropathy
Project ends in 1987

Dyck, Peter J.
Mayo Foundation
Rochester, Minnesota
Mayo Peripheral Neuropathy Clinical Research Center
Project ends in 1987

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders and Stroke

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NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders and Stroke

For carrying out section 301 and title IV of the Public Health Service Act with respect to neurological and communicative disorders and stroke, [$433,595,000] *$339,351,000 (Department of Health and Human Services Appropriation Act, 1986.)*

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders and Stroke

Amounts Available for Obligation[1]

	1985 Actual	1986 Estimate	1987 Estimate
Appropriation....................	$396,885,000	$433,595,000	$399,351,000
Enacted administrative reduction......................	---	-233,000	---
Sequester order..................	---	-18,635,000	---
Proposed rescission.............	---	-9,554,000	---
Subtotal, adjusted appropriation.................	396,885,000	405,173,000	399,351,000
Comparable transfer to:			
Office of the Assistant Secretary for Health, for AIDS Projects.................	-1,168,000	-1,435,000[2]	---
National Cancer Institute for changes in the Central Services financing mechanisms and formulas.......	-1,024,000	---	---
Subtotal, adjusted budget authority..........	394,693,000	403,738,000	399,351,000
Unobligated balance lapsing.....	-715,000	-268,000	---
Total Obligations...............	393,978,000	403,470,000	399,351,000

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[1] Excludes the following amounts for reimbursable activities carried out by this account: 1985 -- $251,000; 1986 -- $600,000; 1987 -- $2,175,000 of which $1,575,000 is for Acquired Immune Deficiency Syndrome (AIDS) projects.

[2] Comparable amount for the appropriation is $1,500,000.

National Institute of Neurological and Communicative Disorders and Stroke

Budget Mechanism
(Dollars in thousands)

Research Grants	1986 1/ 2/ Appropriation		1986 1/ 3/ Available After Sequestering		1986 1/ 3/ Revised Estimate		1987 Estimate	
	Number	Amount	Number	Amount	Number	Amount	Number	Amount
Research Projects:								
Noncompeting projects..........	1,273	188,114	1,273	180,025	1,273	180,025	1,313	188,941
Administrative supplementals...	(33)	1,000	(32)	957	(32)	957	(23)	668
Competing projects:								
Competing renewals...........	282	56,374	282	53,950	270	50,067	223	41,230
New..........................	354	47,917	354	45,849	318	40,202	307	38,346
Supplemental.................	9	695	9	665	9	641	8	550
Subtotal, competing.......	645	104,986	645	100,464	597	90,910	538	80,126
Subtotal, research projects...	1,918	294,100	1,918	281,446	1,870	271,892	1,851	269,735
Research Centers:								
Specialized/comprehensive ctrs.	38	30,150	38	28,853	38	28,853	38	26,371
Subtotal, research centers...	38	30,150	38	28,853	38	28,853	38	26,371
Other Research:								
Research career programs.......	226	12,405	216	11,872	216	11,872	216	11,872
Cooperative clinical research..	1	1,000	1	957	1	957	1	957
Minority Biomedical Support....	(1)	200	(1)	191	(1)	191	(1)	191
Other research related.........	21	1,977	19	1,786	19	1,786	19	1,892
Subtotal, other research.....	248	15,582	236	14,806	236	14,806	236	14,912
Total, Research Grants.........	2,204	339,832	2,192	325,105	2,144	315,551	2,125	311,018

Training	1986 1/ 2/ Appropriation Number	1986 1/ 2/ Appropriation Amount	1986 1/ 3/ Available After Sequestering Number	1986 1/ 3/ Available After Sequestering Amount	1986 1/ 3/ Revised Estimate Number	1986 1/ 3/ Revised Estimate Amount	1987 Estimate Number	1987 Estimate Amount
Individual awards								
Noncompeting	130	2,861	130	2,861	130	2,861	98	2,180
Competing, new..............	78	1,640	69	1,446	69	1,446	101	2,127
Subtotal, Individual.......	208	4,501	199	4,307	199	4,307	199	4,307
Institutional awards								
Noncompeting	369	7,555	369	7,555	369	7,555	297	6,114
Competing, new.............	48	1,097	30	725	30	725	102	2,166
Subtotal, Institutional....	417	8,652	399	8,280	399	8,280	399	8,280
Total, Training..............	625	13,153	598	12,587	598	12,587	598	12,587
Research & Development Contracts.	67	13,102	64	12,539	64	12,539	60	11,529
					FTEs		FTEs	
Intramural Research..............		48,625		46,532	458	46,532	458	47,804
Research Management and Support.........................		17,150		16,261	209	16,261	209	16,413
TOTAL......................		431,862		413,024	667	403,470	667	399,351

[1] Reflects an enacted administrative reduction of $233,000.

[2] Reflects a comparable transfer of $1,500,000 to the Office of the Assistant Secretary of Health (OASH) for AIDS projects.

[3] Reflects a comparable transfer of $1,435,000 to the Office of the OASH for AIDS projects and a consultant services withholding (Section 515 of the Treasury-Postal Service Appropriation Act, 1985) of $268,000.

DHHS - National Institutes of Health

National Institute of Neurological and Communicative Disorders and Stroke

Crosswalk - 1986 Appropriation 1/ 2/

(Dollars in thousands)

PROGRAM ACTIVITY	Mechanism								
	Research Grants			Training Programs					
	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management and Support	Total
Biological Basis Research......................	$198,528	---	$ 8,416	$ 4,145	$ 4,941	$ 4,212	---	---	$220,242
Clinical Research...............	95,572	$30,150	7,166	356	3,711	8,890	---	---	145,845
Intramural Research.............	---	---	---	---	---	---	$48,625	---	48,625
Research Management and Support..................	---	---	---	---	---	---	---	$17,150	17,150
TOTAL.....................	294,100	30,150	15,582	4,501	8,652	13,102	48,625	17,150	431,862

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[1] Reflects an enacted administrative reduction of $233,000.

[2] Reflects a comparable transfer of $1,500,000 to the Office of the Assistant Secretary of Health (OASH) for AIDS projects.

DHHS - National Institutes of Health

National Institute of Neurological and Communicative Disorders and Stroke

Crosswalk - 1986 Available After Sequestering 1/ 2/

(Dollars in thousands)

	Mechanism								
	Research Grants			Training Programs					
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management and Support	Total
Biological Basis Research......................	$189,608	---	$ 8,004	$ 3,973	$ 4,734	$ 4,038	---	---	$210,357
Clinical Research................	91,838	$28,853	6,802	334	3,546	8,501	---	---	139,874
Intramural Research..............	---	---	---	---	---	---	$46,532	---	46,532
Research Management and Support....................	---	---	---	---	---	---	---	$16,261	16,261
TOTAL......................	281,446	28,853	14,806	4,307	8,280	12,539	46,532	16,261	413,024

1/ Reflects an enacted administrative reduction of $233,000.
2/ Reflects a comparable transfer of $1,435,000 to the Office of the OASH for AIDS projects and a consultant services withholding (Section 515 of the Treasury-Postal Service Appropriation Act, 1985) of $268,000.

DHHS - National Institutes of Health

National Institute of Neurological and Communicative Disorders and Stroke

Crosswalk - 1986 Revised Estimate 1/ 2/

(Dollars in thousands)

	Mechanism								
	Research Grants			Training Programs					
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management and Support	Total
Biological Basis Research......................	$182,927	---	$ 8,004	$ 3,973	$ 4,734	$ 4,038	---	---	$203,676
Clinical Research................	88,965	$28,853	6,802	334	3,546	8,501	---	---	137,001
Intramural Research.............	---	---	---	---	---	---	$46,532	---	46,532
Research Management and Support..................	---	---	---	---	---	---	---	$16,261	16,261
TOTAL.....................	271,892	28,853	14,806	4,307	8,280	12,539	46,532	16,261	403,470

1/ Reflects an enacted administrative reduction of $233,000.

2/ Reflects a comparable transfer of $1,435,000 to the Office of the OASH for AIDS projects and a consultant services withholding (Section 515 of the Treasury-Postal Service Appropriation Act, 1985) of $268,000.

DHHS - National Institutes of Health

National Institute of Neurological and Communicative Disorders and Stroke

Crosswalk - 1987 Congressional Justification

(Dollars in thousands)

	Mechanism								
	Research Grants			Training Programs					
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management and Support	Total
Biological Basis Research.............	$181,449	---	$ 7,902	$ 3,951	$ 4,730	$ 3,700	---	---	$201,732
Clinical Research.......	88,286	$26,371	7,010	356	3,550	7,829	---	---	133,402
Intramural Research.....	---	---	---	---	---	---	$47,804	---	47,804
Research Management and Support..........	---	---	---	---	---	---	---	$16,413	16,413
TOTAL.............	269,735	26,371	14,912	4,307	8,280	11,529	47,804	16,413	399,351

National Institute of Neurological and Communicative Disorders and Stroke

Summary of Changes

1986 Current estimated obligations	$403,470,000
1987 Estimated obligations	399,351,000
Net change	-4,119,000

	1986 Base	Change from Base
Increases:		
A. Built-in:		
1. Within grade increase	26,462,000	+ 377,000
2. Federal Employees Compensation Fund increase	101,000	+21,000
3. Unemployment compensation increase	51,000	+2,000
4. FTS rate increase	560,000	+121,000
5. Payment for centrally furnished services	18,752,000	+1,058,000
6. Increased cost of laboratory supplies, materials and other expenses	17,579,000	+738,000
Subtotal	--	+2,317,000
B. Program:		
1. Research projects:		
a. Noncompeting continuations converting from competing status	181,354,000	+93,020,000
b. Competing (new, renewals and supplementals)	90,538,000	+96,492,000
2. Research centers:		
a. Noncompeting continuations converting from competing status	24,067,000	+5,077,000
b. Competing	4,786,000	+5,405,000
3. Other research:		
a. Noncompeting continuations converting from competing status	11,622,000	+3,363,000
b. Competing (new and renewals)	3,184,000	+1,517,000

Summary of Changes -- Continued

	1986 Base	Change from Base
4. Individual training awards:		
a. Noncompeting continuations converting from competing status....................	2,861,000	+1,112,000
b. Competing (new and renewals).................	1,446,000	+2,127,000
5. Institutional training awards:		
a. Noncompeting continuations converting from competing status....................	7,555,000	+773,000
b. Competing (new and renewals).................	725,000	+2,166,000
Subtotal.............	--	+211,052,000
Total increases....	--	+213,369,000
Decreases:		
A. Program:		
1. Research projects:		
a. Noncompeting completed or converting to competing status....................	181,354,000	-51,575,000
b. Competing completed or converting to non-competing status..........	90,538,000	-90,538,000
c. Negotiated reductions......	271,892,000	-42,504,000
d. Reduction in institutional indirect costs...........	271,892,000	-7,052,000
2. Research centers:		
a. Noncompeting completed or converting to competing status....................	24,067,000	-3,133,000
b. Competing completed or converting to non-competing status..........	4,786,000	-4,786,000
c. Negotiated reductions.......	28,853,000	-4,387,000
d. Reduction in institutional indirect costs.............	28,853,000	-658,000

Summary of Changes - continued

	1986 Base	Change from Base
3. Other research:		
a. Noncompeting completed or converting to competing status....................	11,622,000	-1,505,000
b. Competing completed or converting to non-competing status..........	3,184,000	-3,184,000
c. Negotiated reductions.......	14,806,000	-85,000
4. Individual training awards:		
a. Noncompeting completed or converting to competing status....................	2,861,000	-1,793,000
b. Competing completed or converting to non-competing status.......	1,446,000	-1,446,000
5. Institutional training awards:		
a. Noncompeting completed or converting to competing status.....................	7,555,000	-2,214,000
b. Competing completed or converting to non-competing status...........	725,000	-725,000
6. Research and development contracts:		
a. Continuation...............	12,539,000	-756,000
b. Reduction in institutional indirect costs...........	12,539,000	-254,000
7. Intramural research: Program decrease in lower priority areas........................	46,532,000	-520,000
8. Research management and support: Program decrease in lower priority areas......	16,261,000	-373,000
Subtotal, program...........	--	-217,488,000
Total, decreases...............	--	-217,488,000
Total, net change....................	--	-4,119,000

National Institute of Neurological and Communicative Disorders and Stroke

Budget Authority by Activity
(Dollars in thousands)

	1986 1/2/ Appropriation	1986 1/ 3/ Available after Sequestering	1986 1/3/ Revised Estimate		1987 Estimate	
			FTEs	Amount	FTEs	Amount
Biological basis research...........	$220,242	$210,357	---	$203,676	---	$201,732
Clinical research...........	145,845	139,874	---	137,001	---	133,402
Intramural research...........	48,625	46,532	458	46,532	458	47,804
Research management and support........	17,150	16,261	209	16,261	209	16,413
Total Obligations......	431,862	413,024	667	403,470	667	399,351
Unobligated balance, lapsing............	---	268	---	268	---	---
Total budget authority........	431,862	413,292	667	403,738	667	399,351

1/ Reflects an enacted administrative reduction of $233,000.
2/ Reflects a comparable transfer of $1,500,000 to the Office of the Assistant Secretary of Health (OASH) for AIDS projects.
3/ Reflects a comparable transfer of $1,435,000 to the Office of the OASH for AIDS projects and a consultant services withholding (Section 515 of the Treasury-Postal Service Appropriation Act, 1985) of $268,000.

[illegible]S

National Institute of Neurological and Communicative Disorders and Stroke

Obligations by Object

	1985 Actual	1986 Estimate	1987 Estimate
Total number of full-time permanent positions............................	553	553	553
Total compensable workyears:			
Full-time equivalent employment.......	691	693	693
Full-time equivalent of overtime and holiday hours..........	7	7	7
Average ES salary......................	$ 66,232	$ 66,232	$ 66,232
Average GS grade........................	9.14	9.14	9.14
Average GS salary......................	28,224	28,224	28,224
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207).......	35,361	35,361	35,361
Average salary of ungraded positions....	23,206	23,206	23,206
Personnel compensation:			
Permanent positions..................	$ 14,665,000	$ 15,198,000	$ 15,962,000
Positions other than permanent........	6,132,000	6,224,000	6,516,000
Other personnel compensation..........	759,000	755,000	790,000
Special personnel services............	976,000	1,220,000	1,272,000
Subtotal, personnel compensation....	22,532,000	23,397,000	24,540,000
Personnel benefits....................	2,976,000	3,015,000	3,159,000
Benefits for former employees...........	39,000	50,000	52,000
Travel and transportation of persons....	940,000	880,000	942,000
Transportation of things................	89,000	81,000	90,000
Rent, communications and utilities......	1,974,000	1,789,000	1,990,000
Printing and reproduction...............	449,000	441,000	472,000

	1985 Actual	1986 Estimate	1987 Estimate
Other services:			
Project contracts	14,163,000	12,539,000	11,529,000
Centrally furnished services	17,238,000	17,781,000	18,839,000
Standard level user charge	586,000	971,000	971,000
Other	9,821,000	5,915,000	5,592,000
Supplies and materials	4,452,000	4,024,000	4,323,000
Equipment	4,786,000	4,447,000	3,245,000
Grants, subsidies & contributions	313,931,000	328,138,000	323,605,000
Interest and dividends	2,000	2,000	2,000
Total	393,978,000	403,470,000	399,351,000

National Institute of Neurological and Communicative Disorders and Stroke

Significant Items in House and Senate Appropriations Committee Reports

Item	Action to be Taken
1986 House Report	
Batten's Disease Research	
1. "The Committee reiterates its concern about research on Batten's disease, and requests that the Institute actively solicit applications of quality for research on Batten's disease." (p. 54)	1. The Institute supports research directly related to Batten's disease in its laboratories in Bethesda and in research institutions around the world. The Institute hopes to receive other high quality applications for new research grants investigating the disease. In July 1985, the NINCDS issued a Program Announcement requesting applications for Multidisciplinary Research Centers for the Study of Neurogenetic Disorders of Infancy and Childhood. Batten's disease is explicitly noted in this solicitation.
Epilepsy Research	
2. "The Committee urges the Institute to consider supporting additional Comprehensive Epilepsy Research and Training Centers. The Institute is also requested to explore other ways in which epilepsy research might be strengthened." (p. 55)	2. The Institute is supporting three Comprehensive Epilepsy Research and Training Centers through the grant mechanism and continues to attempt to increase the number of projects in epilepsy research. In fiscal year 1985, more epilepsy projects were funded. The Institute has issued four Program Announcements, most recently one entitled "Basic Mechanisms of the Epilepsies," to encourage investigators to submit applications on several areas of epilepsy research. In addition, the NINCDS is using the Small Business Innovative Research Program to fund the development of epilepsy-related technologies.

Item	Action to be Taken
Report on Hearing and Balance Disorders	
3. "The Committee requests, before next year's hearings, an overview of the scope and level of Federally-assisted research on hearing and balance disorders, encompassing research supported not only by the National Institutes of Health, but also by other Public Health Service agencies, the National Science Foundation, the National Aeronautics and Space Administration, the Veterans Administration and the Department of Defense." (p. 54)	3. A report will be submitted to the Committee before the 1987 hearings.

Item	Action to be Taken
1986 Senate Report	
Epilepsy Research	
1. "The Committee directs the Institute to explore ways of supporting additional comprehensive epilepsy research and training centers. The Institute is also directed to explore more effective ways to reverse the trend which has seen epilepsy research funding grow by only 25 percent between 1978 and 1984 compared with 90 percent growth in the overall NINCDS budget." (p. 80)	1. Three Comprehensive Epilepsy Research and Training Centers are being supported through the grant mechanism. The Institute has been and is attempting to increase the number of projects in epilepsy research. In fiscal year 1985, more epilepsy projects were funded. The Institute has issued four Program Announcements, most recently one on the "Basic Mechanisms of the Epilepsies," to encourage investigators to submit applications in several areas of epilepsy research. In addition, the NINCDS is making awards under the Small Business Innovative Research Program to fund the development of new epilepsy-related technologies.
Report on Hearing and Balance Disorders	
2. "The Committee is interested in receiving an overview of the scope and level of NIH support of hearing and balance disorders. This overview should include what is spent on deaf research; a historical look at deaf research and funding; projections on spending for deaf research; and what deaf research projects are currently being funded and where these projects are being conducted. The report should be made available before the fiscal year 1987 hearings on the Institute's budget." (p. 78)	2. A report will be submitted to the Committee before the 1987 hearings.

Item	Action to be Taken
Report on Latent Effects of Polio	
3. "It has come to the attention of the Committee that many of the 300,000 Americans stricken by polio in the 1950's are once again suffering from muscle weakness and excruciating pain. Therefore, the Committee directs NINCDS, in consultation with CDC, to inform the Committee prior to the fiscal year 1987 budget hearings regarding the research efforts which are being conducted in this area." (p. 79)	3. A report will be submitted to the Committee before the 1987 hearings.

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological and Communicative Disorders and Stroke

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1986 Amt. Authorized	1986 Estimate	1987 Amt. Authorized	1987 Budget Request
Research and Investigation..	Section 301	42§241	Indefinite	$390,883,000	Indefinite	$386,764,000
National Institute of Neurological Disorders and Stroke	Sections 457-459	42§285j	Indefinite		Indefinite	
National Research Service Awards......................	Section 487	42§288	$244,000,000[1]	12,587,000	$266,000,000[1]	12,587,000
Total Budget Authority......				403,470,000		399,351,000

[1] This training authority is shared with other research training programs of the National Institutes of Health; the Alcohol, Drug Abuse, and Mental Health Administration; and the Health Resources and Services Administration. Authorization for FY 1986 was contained in the appropriation.

National Institute of Neurological and Communicative Disorders and Stroke

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation[1]
1978	163,059,000	176,438,000	180,438,000	178,438,000
1979	180,932,000	188,910,000	225,000,000	212,365,000
1980	212,652,000	240,622,000	242,000,000	241,966,000
1981	248,941,000	251,382,000	252,240,000	252,533,000
1982	243,017,000[2]	277,720,000	282,211,000	265,901,000
1983	274,505,000	294,361,000	297,077,000	297,056,000
1984	300,631,000	327,368,000[3]	321,160,000[3]	334,952,000
1985	342,409,000	377,328,000[4]	399,211,000	394,693,000
1985 Proposed Rescission	-462,000			
1986	373,782,000	416,857,000[5]	426,784,000	431,862,000
1986 Sequester	-18,635,000			
1986 Proposed Rescission	-9,554,000			
1987	399,351,000			

[1] Reflects enacted supplementals, rescissions, and reappropriations.

[2] Reflects the September Amendment; the original request was $276,156,000.

[3] Excludes $9,512,000 in NRSA training programs not considered.

[4] Excludes $9,209,000 in NRSA training programs not considered.

[5] Excludes $13,153,000 in NRSA training programs not considered.

National Institute of Neurological and Communicative Disorders and Stroke

Justification
(Dollars in thousands)

	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate		1987 Estimate	
			FTEs	Amount	FTEs	Amount
Biological basis research...	$220,242	$210,357	--	$203,676	--	$201,732
Clinical research...	145,845	139,874	--	137,001	--	133,402
Intramural research...	48,625	46,532	458	46,532	458	47,804
Research management and support	17,150	16,261	209	16,261	209	16,413
Total.....	431,862	413,024	667	403,470	667	399,351

General Statement

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) supports and conducts research and research training to further the understanding of the normal and disordered function of the nervous system, (including the brain, spinal cord, and peripheral nerves), muscles, hearing and human communication. Such disorders are numerous and varied; some are among the leading causes of death, but the majority are characterized by long-term disabilities which markedly impair the quality of life. These disorders strike all ages from the disorders of early life like spina bifida, cerebral palsy, Tay-Sachs disease, muscular dystrophy, and meningitis; through the disorders of youth and early adult life such as epilepsy, myasthenia gravis, head and spinal cord injuries, and multiple sclerosis; to the afflictions of adult life and the elderly, including stroke, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis and the dementias including Alzheimer's disease. Across this spectrum must be placed the disorders of communication, hearing, speech, and language such as: congenital deafness in the child, deafness acquired from infections or ototoxic drugs at any age, and presbycusis or the dimming of hearing acuity in the older adult; the language-impaired child and the aphasic adult; and the varied impairments of speech including cancer of the vocal cords and larynx.

Research and Research Training Programs

1. Biological basis research.--This program includes research on the fundamental structure and function of the brain and the nervous system; the causes and pathophysiology of dysfunctions of the nervous system and human communication and research training in the basic communicative sciences and basic neurological sciences.

2. Clinical research.--Research is directed towards the solution of clinical problems directly relevant to patients, including improved methods of disease prevention; improved methods of diagnosis; development of therapeutic interventions including drug and surgical developments and evaluations; development of neural prosthetic devices; epidemiological research, and research training in the clinical neurological and communicative sciences.

3. Intramural research.--The research efforts of this program range from fundamental studies on nerve and associated cell development, structure, and function to clinical research studies aimed at improved methods for the diagnosis, treatment, and prevention of neurological and communicative disorders. The basic approaches involve molecular genetics, cell biology, neurochemistry, and biophysics. The clinical investigations utilize viral, immunological, epidemiological, medical and neurosurgical studies directed toward the prevention or treatment of disorders of the nervous system including those caused by Acquired Immune Deficiency Syndrome (AIDS). Research using brain imaging techniques examines the metabolic and anatomic changes in brains of patients with brain tumors, epilepsy, stroke, Alzheimer's disease, Parkinson's disease and other disorders of the nervous system and the process of human communication.

Overall Budget Policy

The 1987 budget request for the NINCDS is $399,351,000, a decrease of $4,119,000 below the 1986 comparable revised estimate level.

The NINCDS 1987 budget request for research project grants is $269,735,000, a decrease of $2,157,000 from the 1986 revised estimate. The total number of research project grants awarded in 1987 will be 1,851, a decrease of 19 from the 1986 level. These levels will be achieved by limiting indirect cost and by negotiating direct costs downward. The request will support 538 competing project grants at an average cost of $148,930. This represents a 0.4 percent increase in direct costs from 1986 and a 17.4 percent reduction from full recommended levels. Historically, these reductions have averaged 3 to 4 percent. The request will support 1,313 noncompeting project grants at an average cost of $143,900. This represents a 4.4 percent increase in direct costs over 1986 and a 12.7 percent reduction from full commitment levels. Historically, these reductions have averaged 1 percent.

In FY 1986, the Institute will support 38 centers after negotiated reductions of approximately 4 percent. Funds have been requested to support 38 centers in 1987 after negotiated reductions of approximately 14 percent.

Other research grants will be maintained at the same number of awards as the 1986 level. For National Research Service Awards, an estimated 598 research trainees will be supported in FY 1986 and the same number will be supported in FY 1987.

Research and development contracts will be reduced $1,010,000 from the 1986 dollar level, resulting in a reduction of 4 contracts to a level of 60 in 1987 for $11,529,000. R & D contracts for 1987 reflect a reduction of approximately 10 percent in institutional overhead costs.

The 1987 budget request for intramural research is $47,804,000, an increase of $1,272,000 over the 1986 level. The request for research management and support is $16,413,000, an increase of $152,000 over the 1986 dollar level.

The request excludes $1,575,000 for AIDS, which are under the single AIDS appropriation in OASH. Comparable amounts for 1986 are $1,435,000 and for 1985 $1,168,000.

Program Accomplishments

1. Neurological Disorders

Progress continues on the isolation and analysis of the gene for Huntington's disease. The innovative methodologies developed for Huntington's disease are being applied to the study of other neuro-genetic disorders such as neurofibromatosis.

Research into pathogenesis and treatment of Parkinson's disease has been activated by the new model provided by MPTP, a designer drug relative of drugs of abuse which selectively injures the same cells in the brain which degenerate in Parkinson's disease. Selective cell death after injection of MPTP is seen in several animal model systems and is being used as a model to study the pathogenetic mechanisms and to develop new treatments.

Neuroanatomical research with the selective monoclonal antibody tagging of neuro-transmitter molecules and their receptors has led to new insights into Alzheimer's disease. Alzheimer's disease appears to result from the progressive destruction of specific connections between deep brain structures and the elements of the surface (cortex) of the brain, involved in higher mental functions such as memory and learning. The basis of this selective destruction is the subject of intensive study. Efforts have been directed to understanding how the characteristic pathological changes result from intracellular events. Monoclonal antibody techniques have permitted distinguishing between normal cell elements and those abnormal ones seen in Alzheimer's disease.

Active clinical studies for the treatment of multiple sclerosis are underway on interferon, on other modalities which suppress or modulate the immune response, and on drugs of more uncertain mechanisms of action. One promising drug in the latter category is Copolymer-I which has shown promising effects in a small group of MS patients who experienced significant reduction in the frequency of relapses.

Results of research to test the hypothesis that blocking calcium entry into presynaptic nerve terminals would reduce injury indicate that the systemic administration of a calcium antagonist that becomes highly concentrated in the brain prevents morphologic damage to the area affected by hypoxia or ischemia.

Transmission in the central nervous system is a complex process involving movement of ions such as calcium, sodium, and potassium, and of neurotransmitters like gamma aminobutyric acid (GABA) and glycine, which act at junctions between neurons. Considerable evidence indicates epilepsy is associated with alterations in ion movement and imbalances in neurotransmitters. Several new chemical compounds, which act specifically on ionic movement and neural transmission, have been clinically evaluated for antiepileptic efficacy in seizure patients.

The electroencephalogram is a measure of electrical potentials produced by cells at the surface of the brain. Cells deep within the brain produce magnetic fields which may be measured by a new technique called magnetoencephalography (MEG), which can provide information about the location, depth, and orientation of currents within an epileptic focus. Improved technology to refine further the MEG has been developed.

Metabolic studies in Reye's syndrome have demonstrated that elevated amounts of certain neurotransmitters in the blood are a common abnormality found in patients when admitted to the hospital. Observations strongly suggest a specific relationship between these elevations and increased pressure within the brain. These important findings may shed light on the mechanism of brain swelling and provide a biochemical indicator of disease severity.

In a continuing study of hormonal receptors associated with neurofibromatosis, it was found that antiestrogens inhibit the development of certain tumors induced by estrogens.

Studies in metachromatic leukodystrophy, a hereditary lipid storage disorder which shows degeneration of brain white matter, have shown that a specific enzyme activator deficiency causes a disease as devastating as deficiency of the enzyme itself. This activator is involved not only in metachromatic leukodystrophy but also in GM1 gangliosidosis (Gaucher's) and Fabry's disease.

Tourette's syndrome and obsessive compulsive behavior seem to be etiologically related. However, tics are more frequent in males while obsessive compulsive behavior is more frequent in females. Other studies of hormonal control of brain development have found that neurotransmitters influence the growth of certain brain areas that differ in males and females. The metabolically active brain areas associated with vocalization in cats have been identified; high activity in pre-frontal and frontal cortex of the brain is of particular interest regarding the vocal tics in Tourette's syndrome.

A workshop on Rett's syndrome brought together international experts on this developmental disorder to identify promising areas of research which may provide a better understanding of the disorder. The research findings presented at this symposium are being published to permit dissemination of the information to clinicians throughout the world. In addition, at this meeting, Voluntary Health Organizations interested in Rett's syndrome developed procedures by which interested investigators can contact families with Rett's syndrome patients. This interaction will facilitate clinical research in this disorder.

Investigations in head injury research have developed, in collaboration with those in stroke research, a model for experimental subarachnoid hemorrhage to explore events in experimental head injury relative to the clinically devastating phenomenon of vasospasm.

In pain research, the neurons adjacent to the central canal of the spinal cord, have been shown to be specifically responsive in recognition of noxious stimuli as being undesirable or threatening.

An investigator of spinal biomechanics has developed rigid body models for trunk forces that have become the world standard for research and are in use for the study of industrial injuries and low-back pain. Recently, the general applicability of the techniques to modeling very complex tasks has been demonstrated.

Magnetic resonance imaging (MRI) shows great promise for providing information about brain changes early in the course of several diseases, specifically in stroke.

Measurements of local cerebral metabolic rate of glucose using positron emission tomography (PET) yields highly specific information about brain function in patients with brain disorders, including stroke. At present, such measurements require the patient to lie still for several hours. Now an investigator has shown that use of a specific mathematical analysis gives reliable measurements of metabolic rate from PET studies that last for only an hour.

Efforts continue to extend our understanding of how chemicals modify and regulate the functions of the brain. Some of these chemicals allow a single nerve cell to communicate directly with another while others exert an indirect and more generalized influence upon the reactions of many nerve cells. The specific identification of such active effector substances has been aided by new immunochemical techniques to detect and measure transient, minute, and highly localized chemicals. New approaches show microscopic sites on cells where specific receptors identify and respond to specific hormone and transmitter peptides. Through the use of new pathway tracing techniques in the brain, scientists are gaining new understanding of how we perceive pain and some of the intrinsic brain processes that deal with pain perception. There are localized brain systems which both recognize and reduce the distress of bodily pain through intrinsic chemical modulation. These studies have led to new understanding of the mode of action of drugs and are stimulating more rational approaches to new drug development.

Recent developments in producing extraordinarily specific detector molecules (monoclonal antibodies) have provided new insights into pathological as well as normal structure and function of the brain. Many variables modify autoimmune encephalitis (EAE), an important animal model for multiple sclerosis and related disorders of the human nervous system including several quite different antigens, the genetic makeup of the animal, and degree of damage to the nervous system caused by the inflammatory response. Monoclonal antibodies are used to dissect this process and parallel efforts apply results derived from animal models to relevant conditions in patients.

Studies of specific toxic chemicals, some of industrial origin, others from plants, have identified several useful animal models of amyotrophic lateral scerlosis (ALS), with specific degeneration of discrete motor pathways in spinal cord and motor nerves.

Implanting neural tissue into severed spinal cord might yield functional recovery. In animal studies, implants of dorsal root ganglia placed in the injured spinal cord are viable three months after implantation, and the neurons within the implant appear to develop normally.

The critical period, in terms of the age of the tissue implanted into the brain and its ability to make anatomical connections with the adult host, has been determined. Investigators can now begin identifying and manipulating the factors crucial for more successful implantation and growth in animal models.

Glial (neural support) cells contribute to scar formation after spinal cord injury and present an obstacle to regenerating neurons. Steroids, given in appropriate doses, appear to modify scar formation thereby providing a lead toward a better understanding of the management of spinal cord injury.

A study to determine the maximum reasonably tolerated dose of naloxone in stroke patients has been completed, and the maximally tolerated dose can now be tested to determine whether it is effective in reducing the neurological consequents of stroke.

Several groups are using PET to study patients with cerebral infarction and cerebral vascular insufficiency. Several different but identifiable patterns of altered blood flow and metabolism may be observed. These physiological derangements typically precede the clinical onset of a stroke and in some instances may be used to predict tissue injury.

A major clinical trial to evaluate the efficacy of a commonly performed surgical procedure (extracranial-intracranial bypass) has demonstrated that surgery neither improves the outcome of patients with strokes nor prevents additional strokes in stroke prone patients.

Research on the information processing by learning disabled children has shown that electrical brain waves in response to specific stimuli differentiate between reading disability and attention deficit disorder and also between subtypes of reading disability

An analysis of electrical brain waves in response to specific stimuli in autistic adolescents with high functional capacities points to a defect in the brain mechanism for a self-generated, sustained focus of internal attention.

An animal model of an inherited carbohydrate storage disease has been used to purify and characterize relevant enzymes and to provide prenatal detection of the accumulated carbohydrate.

Studies of diabetic rats suggest that decreased blood flow is a likely mechanism for the development of nerve dysfunction associated with diabetes. Non-diabetic rats exposed to prolonged oxygen deprivation developed nerve conduction abnormalities typical of diabetic rats, whereas development of abnormal conduction was delayed in diabetic rats given supplemental oxygen.

Specific and highly controlled infections in animals caused by adapted or attenuated viruses can simulate important neuro-degenerative diseases in humans and lead to new understanding of the predilection for nervous tissue and ways to control and prevent this.

A major area of recent interest has been called molecular mimicry. An infectious agent, viral or bacterial, or its components, bears significant chemical similarity to natural substances within the host's tissues. This molecularmimicry may lead the host's immune response not only to beneficial defense but to harmful effects on the normal host tissues. Thus, just as with damage to the heart and joints in rheumatic conditions, responses to specific infectious agents may produce chronic and progressive damage to the nervous system in demyelinating disorders such as multiple sclerosis.

Much investigation gained new understanding of the peculiar natural animal diseases characterized as slow virus infections. In humans, these have included kuru and Creutzfeldt-Jakob disease; in animals, scrapie of sheep and visna, a demyelinating disease naturally occurring in goats. New findings show striking chemical relationships of the visna agent to the human retrovirus HTLV-III which is the cause of AIDS. The peculiar brain tissue affection and resultant neurological disorders associated with AIDS are better understood as a result of studies of analogous infections in animal models.

Research on the circadian (24 hour) cycles of sleep and wakefulness has identified certain brain cells which maintain and time rhythmic cycles of behavior. These pacemaker nuclei have important influences on sleep, food intake, and hormonal regulation. Basic understanding of these all-pervasive processes are leading to new insights concerning such diverse subjects as sleep disorders, "jet lag," and the optimal dose timing in drug therapy.

Research in behavioral neurology seeks to correlate changes in human perception, cognition, and memory with neurological disease and neuropathology. The inability of patients to recognize familiar faces (prosopagnosia) has been shown to be characterized by bilateral lesions in the temporal cortex. Also, the brains of some Alzheimer's disease patients demonstrate relatively localized neuropathology which appear to "isolate" the hippocampal formation--an area of the brain implicated in memory.

It is now well established that the two cerebral hemispheres differ from each other both functionally and anatomically. For most individuals, language and verbal skills are primarily localized in the left hemisphere while spatial and abstract conceptualization is carried out by the right hemisphere. It has recently been established that the brain of the left-handed person possesses a larger corpus callosum. This large band of fibers connects corresponding parts of the two hemispheres. The results are thought to be consistent with the fact that left-handed people seem to recover faster from strokes than right-handers. This advantage may result from more extensive interconnections between the two hemispheres.

Event-related potentials can be recorded from the scalp of humans and animals. Unlike the electroencephalograph which reflects global brain activity, and different from evoked potentials which reflect the arrival of sensory impulses in the cortex, event-related potentials are correlated with higher cognitive or psychological functions, such as decision-making, attention, and unexpected stimuli. They may differ with the nature of the psychological test, can be evoked by sign language, and may be very long lasting. The technique may be utilized to determine at what point in time perceptions of shape, size and color are registered in consciousness.

Changes in immunological responsiveness result from lesions in various brain areas and can be produced by classical methods of conditioning. Both suppression and augmentation of the immune response as well as the release of histamine from mast cells can be conditioned. Hormones elaborated by the thymus gland as well as peptides produced by white blood cells may influence the activity of the central nervous system. Studies of such interrelationships between the nervous system and the immune system enhance our understanding of both.

2. Communicative Disorders

New measurement techniques have been developed for the assessment of hearing for very high-pitched sounds, thus improving our audiometric diagnostic capabilities. These will permit earlier recognition of hearing losses caused by noise or drug-exposure and lead to better understanding of the subtle effects of aging on the hearing mechanism.

Remarkable progress has been achieved in the processing of speech sounds by hearing aids. One achievement that promises improved reception of speech for all hearing aid users is the suppression of annoying noise in the conversational environment.

Two different cochlear implants for the sensory deaf were given premarket approval by the Food and Drug Administration so these are now available to the deaf. These implants utilized research results and technology developed by the NINCDS neural prosthesis program.

Recent interest in the development of cochlear implants for the profoundly deaf has focused attention on other previously largely neglected methods of communication for the deaf. Compact arrays of vibrators or tactile stimulators have now been developed which, when held for example against the skin of the wrist, can serve to alert the deaf individual wearing the device to the presence of sound in the environment. These tactile arrays can also convey important information about the pitch and loudness of sounds.

The gerbil is now serving as a satisfactory animal model of presbycusis (the hearing impairment associated with aging). The animal has a life-span of three years, making it especially valuable for further studies of the precise causes of presbycusis. A major problem associated with the treatment of various forms of dizziness has been the difficulty of measuring balance function and of detecting disorders of balance. Many of the inaccuracies in current measurement methods will be removed as computerized methods of measuring balance and dizziness will become available for general use in 1986.

Despite many advances in our understanding of the causes of otitis media with effusion, a very common type of ear infection in children, surgery continues to be the main treatment available for the problem. A comparison of available surgical treatment methods is in progress and will be completed in 1986. The results will provide valuable guidance in the treatment of the disease.

Computerized tomographic (CT) scans are providing precise and important information concerning the location and extent of brain damage following strokes and the interference with language processes that may result. Accurate predictions can now be made concerning the potential for recovery of language in those cases where the stroke has interfered with language comprehension. CT scans in stroke victims are also enabling clinicians to select among the various clinical methods of treating aphasia or language loss.

It is now recognized that the small muscles within the larynx responsible for the production of speech do not work as single independent units but that patterns of movement are carried out under central nervous system control. If one muscle does not move to its correct position during speech others immediately adjust their position in order to ensure accurate speech production. These principles will have an important influence on clinical methods of improving abnormal speech production.

3. Research Training and Career Development

The Institute continues to promote and sponsor research training in neurological and communicative processes. These programs develop a cadre of skilled investigators capable of applying the modern research tools of modern biology to the investigation of neuronal mechanisms. Emphasis has been given to training in: 1) basic neurosciences including molecular biology, developmental neurology, neurobiology, neurochemistry, neuroimmunology, neuropharmacology, and neurovirology; 2) basic communicative sciences, including audiology, sensory physiology and biophysics, and speech pathology.

The NINCDS gives special emphasis to the recruitment and research training of clinical investigators in the neurological and communicative disorders. The program supports training for research careers aimed at the development of and the evaluation of improved methods of diagnosis, prevention, therapy and the application of experimental animal research to clinical problems of the human nervous system and human communication. Major clinical areas of research training include: medical neurology, neurosurgery, neuroepidemiology, neuropathology, otolaryngology, audiology, otopathology, and speech pathology.

Career development in a broad spectrum of the areas of research responsibility of the NINCDS has been supported through the Research Career Program which includes Research Career Development Awards (RCDA), and Clinical Investigator Development Awards (CIDA). Former awardees are at the forefront of research on improved diagnostic methodologies, etiology, treatment, and prevention of disorders of the nervous system, the neuromuscular apparatus, the ear, human communication and the special senses of taste, smell, touch and pain. The majority of former awardees have now competed successfully as principal investigators on research project grants. The breadth and depth of their research activities, volume of publications, and advancement in academic positions point toward attainment of Research Career Program goals. In particular, the CIDA has provided a highly effective method for the recruitment and preparation of future clinical investigators in the neurological and communicative disorders.

4. Intramural Research

Positron emission tomography (PET), a method for visualizing the metabolism of the human brain both during normal activities and in disease states has helped in studies to localize and grade malignancy of brain tumors; identify abnormal regions in brains of patients with Alzheimer's disease and epilepsy; and examine areas of the brain involved in movement disorders. Introduction of labelled markers specific for biogenic amines and their receptors has provided a new dimension to study abnormal brain function and effects of drugs on brain.

Research into the clinical diagnosis and management of the epilepsies has shown that changes, possibly deleterious, occur in the metabolism of the brain with certain antiepileptic drugs. Use of PET technology has shown the feasibility of demonstrating drug effects in specific brain areas.

PET has been compared with magnetic resonance imaging (MRI) to assess the relative merits for diagnosis and typing of cerebral tumors. A study on demyelinating disease has unexpectedly found that some patients with clinically definite multiple sclerosis show few lesions whereas other patients with relatively mild clinical symptoms show widely disseminated lesions. Lesions have been seen in an asymptomatic identical twin of a patient with multiple sclerosis. This finding indicates subclinical disease previously suspected from evaluation of the immune response.

The biochemical defects in a number of inherited neurological disorders, of which Gaucher's disease is a familiar example, have been identified. These defects cause a wide variety of neurological problems including mental retardation, dementia, unsteady gait, seizures, and in many patients, early death. The gene for glucocerebrosidase, the enzyme involved in Gaucher's disease, has been cloned. The primary metabolic defect of Type C Niemann-Pick disease is the lack of conversion of cholesterol into an ester compound.

Antibody producing cells have been shown to share antigenic determinants with myelin-associated glycoprotein, explaining the damage to myelin in some autoimmune diseases. As a result of antibody binding, a specific protein is activated which degrades myelin associated protein.

Safe local perfusion of chemotherapeutic agents directly into the blood supplying a brain tumor and the removal of the toxic agent from the venous blood before it can reach the general circulation has reduced the side effects of chemotherapy. New chemotherapeutic techniques include interleukin-2, stimulated lymphocytes, a technique developed by an NINCDS scientist, and toxic ricin molecules attached to monoclonal antibodies that are directed against specific tumors.

MPTP-induced parkinsonism in subhuman primates is being developed as a means for assessing new antiparkinsonian drugs and brain tissue implants to reverse degenerative diseases of the nervous system. A hemi-parkinsonian state can be produced by unilateral internal carotid artery injection of MPTP providing an animal with an intact side of the brain which serves as a unique experimental control.

Proteins have been isolated which direct rapid axonal transport from the nucleus of a neuron to the nerve endings. This Kinesin molecule has been isolated from mammals and monoclonal antibodies have been prepared which can be used as probes in the various neurological diseases involving disorders of the axonal transport system.

Continued study on Creutzfeldt-Jakob disease (CJD) has revealed a worldwide deathrate of one per million per year and the existance of high incidence foci. In familial cases, a single autosomal-dominant gene pattern of occurrence is true in spite of the fact that the disease is caused by a virus. A new immunologic test for the diagnosis of CJD has been developed.

The Institute has initiated the main phase of the application of clinical data banks for research in stroke and in traumatic coma. Investigations from the earlier pilot Traumatic Coma Data Bank have identified specific clinical signs as indicators of poor prognosis in patients with severe head injury who experience a lucid interval prior to coma. The Stroke Data Bank has developed a new diagnostic classification for stroke which will allow for the assessment of prognosis within etiological subgroups of stroke cases. This points to the type of stroke and the location of the stroke lesion as likely indicators of the magnitude of the case fatality rate.

A collaborative effort with the World Health Organization Neurosciences Program, the World Federation of Neurology, and the American Academy of Neurology to revise a standardized, internationally accepted classification and coding system for neurological disorders has been achieved. This system has been shown to be useful for neuroepidemiologic research. Cost effective use has been made of existing registries of neurologic disease, such as in a study of presenile dementia based on the Israeli National Neurologic Disease Registry. In addition, we have collaborated with British investigators in organizing information routinely collected through the British National Health Service on all neurologic inpatients in a section of London with 3-1/2 million inhabitants. The utility and accuracy of these data have been demonstrated in a study of Guillain-Barre' syndrome. A similar registry is being organized for the population of northeastern Italy. The record-linkage system of the Mayo Clinic in Rochester is being used to study neurologic diseases in the population of Rochester, Minnesota.

Acquired Immune Deficiency Syndrome Research

1. Extramural Research

A. 1986 Accomplishments:

The NINCDS has awarded a new research grant for a comprehensive study on the clinical and laboratory aspects of AIDS dementia, the progressive mental deterioration frequently associated with advanced AIDS. The clinical aspects of the study characterize the incidence, early manifestations, neurodiagnostic test profiles, and the natural history of AIDS dementia.

B. 1987 Initiatives:

Studies will focus on the regional distribution of HTLV-III virus within the brain. These studies are expected to yield useful information on the pathogenesis of the dementia. Advanced imaging techniques will be applied to selected well characterized patients for correlation with clinical and pathological findings.

2. Intramural Research

A. 1986 Accomplishments:

The NINCDS has demonstrated that 40 percent of AIDS patients develop brain lesions which contain the AIDS virus. Moreover, humans having antibodies to AIDS virus (HTLV-III/LAV) without clinical AIDS symptoms frequently carry the virus in their brain, and some of them have a neurological disease. Scientists in the NINCDS Intramural Research Program are now testing whether certain drugs can inactivate the AIDS virus in the brain as well as the relationship between the AIDS virus and neurological diseases and brain tumors.

In a collaborative study with non-government investigators, the Institute has demonstrated that the activity of a key brain enzyme is elevated in the red blood cells of patients with AIDS. Studies are in progress to determine the potential value of measurement of the enzyme in patients. This information may be useful as a back-up test to current screening procedures.

The diagnosis of Progressive Multifocal leukoencephalopthy (PML), a frequent complication of AIDS, has been improved by the development of a sensitive immunochemical test that uses modern methods of biotechnology.

A chimpanzee model of persistent infection developed by NINCDS intramural scientists has produced important new knowledge. The chimpanzee model has enabled the scientists to differentiate among stages of the retrovirus infection. Eventually, this work may lead to immunological tests that will differentiate between different stages of infection in human patients. The model may lead to a way to identify patients diagnosed as having AIDS-related complex (ARC) who will ultimately develop clinical AIDS. Furthermore, this information suggests that the interval between the initial infection and the onset of the clinical disease may exceed the 5-year period that is believed to be the upper limit of an asymptomatic incubation period for this virus. The scientists also used the chimpanzee model inoculated with both the French and

United States strains of HTLV-III/LAV retrovirus to test for specific antiviral antibodies. They suspected that these antibodies might be secreted in the cerebral spinal fluid. They discovered such secretions; this finding suggests that the virus entered the brain and is provoking a localized immune response.

In a series of experiments conducted in marmoset monkeys, two animals inoculated with the HTLV-III/LAV virus developed antibodies to the virus and several months later developed a fatal wasting disease. Scientists are studying the tissues from these animals for the presence of the virus and are attempting to serially pass the virus to healthy, previously uninoculated animals of the same species.

B. 1987 Initiatives:

The NINCDS intramural scientists plan to continue their indepth investigations of the mechanism by which the AIDS virus enters the brain. Drugs acting on the AIDS virus will be examined with emphasis on the drugs' effects on the brain where the virus is relatively protected from circulating antibodies. The correlation between increased level of certain antibody enzymes and virus antibody activity will be analyzed as a potential simple testing system. The scientists will attempt to determine the implications of increases in activity of specific enzymes. If, for instance, the increase in activity of an enzyme which was observed in red blood cells in AIDS patients is found to precede certain steps of AIDS or ARC, the enzyme may have significant predictive value.

The ability of drugs to penetrate the blood-brain barrier and inhibit HTLV-III/LAV virus in chimpanzees with persistent infections will be evaluated. If an AIDS infection of the brain is to be attacked, scientists must find a way to enable effective drugs to cross the blood-brain barrier.

We have identified patients with various neurological findings who do not yet have clinical AIDS. These patients have antibody and progressive damage to the nervous system. We will investigate the immune responses, presence of virus and possible approaches to treatment of patients with central nervous system AIDS.

In collaboration with investigators at Georgetown University, D.C. General Hospital and in Chicago, we are studying pregnant women in high-risk groups for AIDS including intravenous drug users, prostitutes, and partners of AIDS patients. Female patients with antibody HTLV-III/LAV will be studied in detail using immunological and virological methods. Babies born to infected mothers will also be included in the investigation.

Cellular immune function including measles-specific cytotoxicity will be evaluated in individuals who have the ARC syndrome, and normals who have antibodies to HTLV-III. Identical studies will be performed in a group of nonpromiscuous male homosexuals. The links between measles, AIDS, and ARC, as well as a broader understanding of the immunology of AIDS, are the underlying target of this research.

National Institute of Neurological and Communicative Disorders and Stroke

Biological Basis Research

1987 Authorization: Indefinite

Budget Authority:

1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987	Increase or decrease
$220,242,000	$210,357,000	$203,676,000	$201,732,000	- $1,944,000

Purpose and Method of Operation

Biological Basis research is primarily responsible for stimulating and supporting research to provide new information on the structure and function of the neurological and communicative systems as a basis for development of methods for disease prevention. The underlying causes of most neurological and communicative disorders are not known at the present time. The disciplines involved include neurobiology, neurovirology, neurophysiology, neuropharmacology, and neurochemistry. More and more, multidisciplinary approaches to basic problems are proving to be productive. Communication among investigators and technology transfer are fostered by selective support of research workshops, symposia and conferences.

Studies of fundamental mechanisms in the nervous system not only provide the key to prevention, but in addition, develop the research techniques and methodologies that are adapted by clinical investigators. Research physicians are often trained in basic laboratories which provide the rationale and methods for studying the pathological process. Support is provided through research grants, Research Career Program awards, research and development contracts, and National Research Service Awards.

The Institute's research training budget supports Individual National Research Service Awards (NRSA) which are exclusively postdoctoral, and Institutional NRSAs which emphasize postdoctoral research training, but also provide support for a limited number of predoctoral trainees in selected research disciplines of national shortage.

Through the Research Career Program, specifically the Research Career Development Award (RCDA), the Institute promotes and supports career development of neurological and communicative scientists. Awards provide stipend support to enhance the research capability of individuals who, in the formative stages of their careers, have demonstrated outstanding potential for contributing as independent investigators to health-related research in the basic sciences.

Rationale for the Budget Request

The 1987 request is $201,732,000, a decrease of $1,944,000 below the 1986 estimate. The following are the program plans for 1987:

1. Neurological Disorders

Over the last decade, advances in the neurosciences have seen the development of new concepts in cell recognition, intracellular communication, and cell-to-cell information transfer. The Institute will support research in cellular and molecular neurosciences which will contribute to the understanding of seizure generation, spread, and arrest. Such understanding is fundamental to more effective prevention, diagnosis, and treatment of seizures.

Status epilepticus is defined as "epileptic seizures that are so frequently repeated or prolonged as to create a fixed and lasting epileptic condition." The Institute will support research programs to obtain a better understanding of the fundamental mechanism of such long-term, repeated neuronal firing and understanding of ways to prevent its consequences.

Over 50 percent of the patients who die of traumatic brain injury die because of increased intracranial pressure, as a result of the brain swelling that often ensues after injury. Investigators will study how the brain handles excess fluid and how this relates to intracranial pressure.

Investigators will study the effects of decreases in regional cerebral blood flow and changes in certain metabolites, soon after injury, that may be responsible for the development, and perhaps spread, of vasogenic edema.

Cerebral ischemia is associated with the degradation of complex membrane fats and an accumulation of free fatty acids. The effects of certain substances (CDP amines) on ischemia induced damage will be studied in an experimental model to test whether stroke induced changes in membrane structure and function can be reversed by controlling lipid metabolism.

Investigators will continue to identify and characterize endogenous factors that promote neuronal growth either during normal development or after injury. The goal is to learn how to regulate these endogenous growth factors in order to promote regeneration after injury.

Getting severed nerves to grow is just a first step; to regain function, they must reconnect to the proper target. Recent studies have shown that there are specific marker molecules in target membranes that may guide correct reconnection. Monoclonal antibodies will be used to identify these markers.

Recent findings show that in chronically paralyzed animals a small percentage of the axons in a severely injured spinal cord still remain and conduct nerve impulses, although abnormally. Future experiments will determine if it is possible, through glial implants or drug treatment, to repair these axons so that they conduct normally, thus making them functional.

New studies will provide a more complete understanding of the cell biology and biochemistry of the supporting cells of the central nervous system. One such type of cell, the astrocyte, has been found to be crucial in guiding neuronal development, in modulating the external environment of neuronal cells during function, and in repairing the nervous system after disease or injury.

Major efforts are continuing in slow virus research with one Senator Jacob Javits Center of Excellence in Neuroscience Research analyzing the unconventional scrapie agent. Related efforts on the visna retrovirus which may provide an important model for AIDS dementia will be supported.

Aged primates have shown some of the changes characteristic of Alzheimer's disease. Research using this analogous animal model will be vigorously pursued to study the interaction of genetic factors and natural aging.

Neural prostheses are aids for the neurologically handicapped which replace or supplement neurological function. During fiscal year 1987, a new project will be initiated on studies in animals to develop approaches to a neural prosthetic cochlear implant for children. Studies will continue on the development of new biomaterials for use in neural prosthetic implants and the development of motor prostheses for control of paralyzed extremities in spinal cord injury victims.

Research in the area of neuroimmunomodulation should elucidate the various feedback mechanisms that modulate interrelationships between the nervous system and immunological responsiveness.

Multidisciplinary studies of synapse structure, function, and development will be aimed at a better understanding of how the nervous system is organized and functions.

Studies will continue to investigate the differentiation and properties of embryonic neural crest cells, an important part of the developing nervous system, which are the source of many different adult cell types. Abnormal development of the neural crest is responsible for many developmental abnormalities of the brain and spinal cord.

Monoclonal antibodies will continue to be extensively used to study gene regulation in nervous system development, cell lineage and interaction, mechanisms of axon interconnection, expression of specific surface antigens and the appearance of specific neurotransmitters.

The metabolic basis and mechanisms of development of a lethal inherited carbohydrate storage disease in a goat model of human disease will be investigated by an interdisciplinary team of veterinarians, pathologists, biochemists and geneticists.

New lines of research involving glutamate, a neurotransmitter, will examine the consequences of disruption of normal glutamate function on brain development.

Using cat vocalization as an experimental approach to Tourette's syndrome, neural pathways and biochemical changes will be traced in association with electrically elicited call behaviors.

The study of undernourished infant rat brains will focus on the optimal nutritional status for developing normal white matter.

Research into the developmental differences between male and female brains will continue to document the relative contributions of sex hormones, neurotransmitters, and anatomic connections to the growth process.

Research will continue to pursue the mechanisms whereby naturally occurring opiates regulate brain growth and development.

Developmental changes in the normally occurring pattern of cell migration, distribution, and death in the brain cortex will be observed after experiments involving damage to neurons both directly and indirectly connected to the cortex.

A Senator Jacob Javits Center of Excellence in Neuroscience Research involving a multidisciplinary research team, equipped with a primate colony and nursery, will continue to examine the developmental neurobiology of the primate neocortex -- its synaptic organization, plasticity and modifiability.

The respective roles and interactions of neuropeptides and other neurotransmitter molecules require further study. New work on how such brain chemicals are affected in important degenerative disorders will be encouraged.

The identification of specific neuropeptides which are involved in discrete pain pathways opens an important area of basic pain research in more specific and safer pharmacologic approaches may be developed for analgesia.

Tying specific T-lymphocytes subtypes to key steps in the immune reaction will be explored as a "handle" for the selective blocking of elements of this complex process in demyelinating disorders.

Development of models using specific toxins which can cause progressive nervous degeneration simulating well known human disorders such as ALS will continue. Studies with these models will improve understanding of the steps in the degenerative process and suggest interventions which may prevent or reverse the damage. The toxic process itself may be important not only as a model for more common disease but to provide environmental alerts to potential hazardous substances.

Research aimed at correlating behaviorally measurable alterations in humans with neuropathological findings will attempt to delineate more precisely the anatomical variations seen in human brains. The neural pathways involved in various aspects of memory and visual perception will be further delineated. These studies will also contribute to an understanding of systems in the brain responsible for color vision, depth perception, language development and maintenance of appropriate social interactions.

Research on the bilateral asymmetry of the human brain should establish whether the larger corpus callosum found in left-handed people consists of more nerve fibers or larger individual fibers, and possible sex differences will be studied. It should be possible to relate levels of verbal performance with characteristics of the left temporal area, and perhaps perceptual skills to aspects of right hemisphere variations.

Detailed studies of event-related potentials should reveal which brain regions and pathways are involved in conscious functions, such as attention and decision making. This research may also lead to a better understanding of the global neural basis of learning disabilities.

A unique animal model, the transparent zebrafish, will be used to study the specificity of synapses between neurons and between neurons and muscle cells. Nerve growth can be directly observed in normals and mutants in an attempt to answer some fundamental questions on the development of the nervous system.

2. Communicative Disorders

Recent research has shown that the inner ear is not a passive receiver and transducer of sound, like a simple microphone, but is able to distinguish between sounds very close in pitch or frequency by a complex process involving active movement of the hair cells. The presence of the hair cells has long been recognized; but only recently has their active, as opposed to passive, role in conversion of sounds into electrical impulses been recognized. Further studies of these mechanisms will provide important information on the basic mechanisms of hearing and on the causes of hearing disorders.

Neurophysiological techniques are being used to determine how speech and language functions activate different regions of the brain in normal adults and in patients with such speech disorders as stuttering and spasmodic dysphonia.

Neuroimaging and positron emission tomography (PET) studies will examine the brain activation patterns of children with language and learning disorders. This new effort is aimed at determining the neurological bases for learning disabilities in children, and at identifying methods of treatment.

The development of some areas of the brain is influenced by early hearing experience; deafness interferes with this process and hence with normal brain development. Electrical brain potentials of individuals deaf since birth, but who are using American Sign Language (a visual language), are different from those of normal hearing individuals during tasks involving the processing of language and non-language materials. Studies in this area will clarify the roles of early sensory (e.g., hearing) and early language experience in brain and behavior development.

3. Research Training and Career Development

The Institute will continue to encourage and support research training on the fundamental structure and function of the brain and nervous system and the causes and pathophysiology of dysfunction in the nervous system and in human communication. Particular emphasis will be placed on studies of speech, hearing, and taste mechanisms; training in basic science areas related to head and spinal cord injury, including neural regeneration and prosthetic research and to neurogenetic disorders.

Through the Research Career Program, the Institute will promote and support the development of promising young scientists in the following areas: audiology, developmental neurology, neurobiology, neurochemistry, neuroimmunology, neuropharmacology, neuroradiobiology, neurovirology, neural regeneration and plasticity, sensory physiology and biophysics and speech pathology.

National Institute of Neurological and Communicative Disorders and Stroke

Biological Basis Research

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987 Estimate
Neurological disorders of early life	$28,098,000	$26,843,000	$25,991,000	$25,736,000
Neurological disorders of adult life	8,015,000	7,657,000	7,414,000	7,341,000
Stroke	7,458,000	7,125,000	6,899,000	6,831,000
Epilepsy	10,202,000	9,747,000	9,437,000	9,345,000
Demyelinating disorders	12,839,000	12,265,000	11,876,000	11,760,000
Neuromuscular disorders	12,139,000	11,597,000	11,229,000	11,119,000
Infectious diseases of the central nervous system	6,481,000	6,192,000	5,995,000	5,937,000
Trauma and injury	21,982,000	21,001,000	20,334,000	20,135,000
Tumors	2,588,000	2,473,000	2,394,000	2,371,000
Disorders due to neurotoxicants	2,350,000	2,249,000	2,188,000	2,150,000
Neuroendocrine & autonomic nervous system	15,179,000	14,501,000	14,040,000	13,903,000
Learning and behavior	5,450,000	5,207,000	5,041,000	4,992,000
Nervous system function	45,880,000	43,824,000	42,415,000	42,064,000
Metabolism and nutrition	2,132,000	2,037,000	1,972,000	1,953,000
Hearing and equilibrium	19,824,000	18,939,000	18,337,000	18,158,000
Speech and language	1,670,000	1,596,000	1,545,000	1,530,000
Other sensory disorders	15,306,000	14,623,000	14,158,000	14,020,000
Multicategorical research	2,649,000	2,481,000	2,411,000	2,387,000
Total	220,242,000	210,357,000	203,676,000	201,732,000

National Institute of Neurological and Communicative Disorders and Stroke

Biological Basis Research

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987 Estimate
Budget mechanism:				
Research Project Grants				
Number	1,505	1,505	1,467	1,452
Amount	$198,528,000	$189,608,000	$182,927,000	$181,449,000
Other Research				
Number	145	138	138	136
Amount	8,416,000	8,004,000	8,004,000	7,902,000
Total, Research Grants				
Number	1,650	1,643	1,605	1,568
Amount	206,944,000	197,612,000	190,931,000	189,351,000
Training 1/				
Individual awards				
Number	192	184	184	183
Amount	4,145,000	3,973,000	3,973,000	3,951,000
Institutional awards				
Number	243	233	233	233
Amount	4,941,000	4,734,000	4,734,000	4,730,000
Total, Training				
Number	435	417	417	416
Amount	9,086,000	8,707,000	8,707,000	8,681,000
R & D Contracts				
Number	25	24	24	22
Amount	4,212,000	4,038,000	4,038,000	3,700,000
TOTAL	220,242,000	210,357,000	203,676,000	201,732,000

1/ Numbers are full-time training positions.

National Institute of Neurological and Communicative Disorders and Stroke

Clinical Research

1987 Authorization: Indefinite

Budget Authority:

1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987	Increase or decrease
$145,845,000	$139,874,000	$137,001,000	$133,402,000	- $3,599,000

Purpose and Method of Operation

Clinical research uses the fundamental knowledge developed by basic research to clarify pathological conditions and to identify and pursue methods for amelioration, therapeutic intervention, and prevention of these conditions. Studies involve not only clinical investigations in humans, but also preclinical research aimed at development of disease models as well as development of a variety of diagnostic tests and prosthetic devices. The purpose of this research is to identify means for eliminating the causes of disorders or to provide more definitive treatment of these disorders. This program activity is supported through research grants, research centers, research career program awards, National Research Service Awards, and research and development contracts.

The Institute provides clinical research training through individual National Research Service Awards (postdoctoral fellowships) and institutional National Research Service Awards (training grants). These programs train personnel for academic careers in research aimed at developing improved diagnosis, treatment and, where possible, prevention of human nervous system and disorders of human communication (hearing and speech). Major areas of research training are: 1) medical neurology, neurosurgery, neuroepidemiology and neuropathology; 2) clinical communicative sciences, including otolaryngology, audiology, otopathology and speech pathology.

The Research Career Program, through Clinical Investigator Development Awards (CIDA), promotes and supports the development of research skills among physician scientists. This program seeks to recruit and prepare future physician investigators for academic research careers in the neurological and communicative sciences. Examples of such clinical areas include neurology, neurosurgery, neuroepidemiology, neuropathology, otolaryngology, audiology, and speech pathology. This award provides candidates with the opportunity for 3 to 5 years of special study and supervised experience tailored to individual capabilities and research interests. Successful applicants are individuals with high potential for academic and/or research careers in clinical areas. These awards bridge the gap between the early postdoctoral period and academic appointment.

Rationale for Budget Request

The 1987 request is $133,402,000, a decrease of $3,599,000 below the 1986 estimate. The following are the program plans for 1987:

1. Neurological Disorders

Modern gene technologies, specifically DNA restriction enzymology and recombinant DNA technology, are being explored as approaches to discovering the genetic basis of certain forms of epilepsy. In order to apply these new technologies, families with several generations of affected individuals must be identified. Clinicians are now combining forces with basic scientists to study the genetics of epilepsy.

The occurrence of epileptic seizures is particularly high during sleep. Sleep is used as a technique to activate abnormal activity in routine brain wave (EEG) recordings. Further, sleep deprivation increases seizure frequency and abnormal EEG findings. The Institute will support research to explore the relationship between epileptic phenomena and different states of sleep and arousal.

Post-traumatic epilepsy occurs in 5-10 percent of head-injured patients (30,000 new cases a year in the United States). Controlled clinical trials to determine whether prophylactic antiepileptic drug therapy can prevent or reduce this high incidence of post-traumatic seizures will continue.

A clinical trial will continue to assess the long-term effect of phenobarbital on intelligence and behavior in young children who are receiving the medication after having a febrile seizure.

A clinical trial aimed at optimal treatment for Tourette's syndrome will continue to compare both the adverse reactions and effectiveness of pimozide and haloperidol.

Studies will continue to focus on possible mechanisms of pathogenesis of Reye's syndrome, including the role of aspirin, which has been implicated in the onset of the severe metabolic derangement characteristic of Reye's syndrome.

The preliminary results of trials of Copolymer-I in multiple sclerosis will be extended to a multi-institutional cooperative clinical trial for definitive evaluation of its safety and effectiveness.

Other therapeutic studies in multiple sclerosis will focus on development of antibodies which can inhibit critical steps in the development and progression of autoimmune demyelination.

The complex metabolic intracellular actions of MPTP, the toxic agent which simulates Parkinson's disease, provide opportunities to block the poison's effects. Such approaches may also be relevant to naturally occurring Parkinson's disease and clinical studies along this line will be encouraged.

The development of positron emission tomography (PET) and other specialized imaging techniques is becoming progressively more sophisticated. Studies of late life degenerative diseases such as Huntington's, Parkinson's, and Alzheimer's diseases are now focused on the earliest changes in presymptomatic subjects at risk to allow early diagnosis and preventive intervention.

The effort to isolate the Huntington's gene will be pursued with increased effort. Bracketing the gene locus with another marker will narrow the scope of search of the collected pedigrees.

Although 70 percent of stroke patients survive an average of seven years, a major limiting factor in the rehabilitation of survivors appears to be affective disturbances. Thus, an understanding of affective disorders in association with lateralized brain injury is very significant. The correlation of physical disability, location of damage, extent of damage, and biochemical alterations, with the affective changes is important in its own right and is an important beginning toward a scientific restructuring of beliefs about affective change in patients with stroke and their potential for therapy.

Clinical studies will test potential new forms of treatment for stroke patients. The new agents are nicardipine, shown in animals to protect the brain during diminished blood flow, and heparinoid, thought to be a safer agent than to prevent the formation of blood clots that cause further strokes.

Studies will be initiated to see if a new drug, tissue plasminogen activator, will be useful as a treatment for stroke if given within a short time after the onset of symptoms.

Cardiopulmonary resuscitation (CPR) results in extraordinary changes in cerebral blood flow and brain oxygen consumption. Research will continue to investigate the optimal parameters of mechanical ventilation and pharmacological support needed to maintain optimal cerebral perfusion pressure without stimulating metabolic demand.

Although it is evident that circulating blood platelets are important in the pathogenesis of stroke, the interrelationship of platelets and the other blood elements in causing pathological thrombus formation leading to stroke is poorly understood. Factors related to blood viscosity will be examined with the focus on the function of red blood cells in various types of strokes.

The extraordinarily complete data base on 1,400 patients in the extracranial-intracranial bypass surgery clinical trial will be studied in detail in an attempt to discover important characteristics of different types of stroke, the presenting features, the course of the disease, and the outcome.

The longitudinal prospective study of an aged population directed at identification of risk factors for the development of dementia will be continued. Attention will be focused on examination of leads generated in early phases of the study such as differences in sex risk, and differential mortality indicators.

A variety of neuromuscular disorders will be explored using new magnetic resonance spectroscopic techniques. Characteristic patterns of metabolic change in patients with these disorders will be determined; other studies may lead to better management and new treatment techniques.

A continuing study will investigate the genetic, biochemical, clinical and pathological aspects of hereditary metabolic disorders of amino acids and related compounds, particularly those that affect brain development and cause mental retardation, seizures, and other neurologic complications.

Abnormal brainstem and cortical evoked responses to a variety of sensory stimuli will be studied in autistic children and adolescents to determine if these children respond differently to such stimuli.

A multidisciplinary, multicentered project will characterize and compare autistic, language-impaired, and mentally retarded preschool children in an effort to standardize and simplify clinical diagnostic categories.

The cause and development of neonatal brain hemorrhage and the extent to which its severity affects brain function in the newborn period and in early childhood is the objective of comprehensive new studies.

The relationship between neurochemical changes in neurotransmitter systems and Attention Deficit Disorder, the most common of the childhood neurobehavioral disorders, will be studied and may lead to a basis for more rational and effective therapy.

Recombinant DNA technology will be used to study the molecular basis of an important new class of genetic diseases presumably encoded by mitochondrial DNA and transmitted maternally, although not by the usual sex-linked genetic mechanism. These include Leber's optic atrophy, infantile bilateral striatal necrosis, mitochondrial myopathy, and chronic external ophthalmoplegia.

A new study will identify the chromosome map location of the genes responsible for various types of neurofibromatosis. It will use the new technique of restriction fragment length polymorphisms to establish linkage relationships in families with these diseases.

2. Communicative Disorders

Recognition of speech has been achieved by profoundly deaf adult patients using electronic cochlear implants. Specific components of the speech spectrum are transmitted as electrical signals to the nerve cells. Speech recognition is an important step toward hearing of conversational speech. A clinical comparison of single and multichannel electronic cochlear implants for the deaf will provide information concerning the optimum design of implants as well as information on the types of persons who can benefit most from the use of these devices.

Studies of speech and language impaired children will lead to improved identification, diagnosis and intervention. Several investigations of children with delayed language development, impaired speech sound production, or autism promise to increase our understanding of the characteristics and underlying bases of these communication impairments.

Development continues on a personal computer-based system for profoundly deaf children. The system is designed to increase the effectiveness of speech training sessions and promote home practice essential for maintenance of speech skills learned in the treatment program.

Increased attention to the incidence and diagnosis of swallowing disorders has demonstrated that such disorders can result from unilateral brain injury. Studies addressing swallowing mechanisms and their neurological control will provide new knowledge for the treatment of patients with swallowing disorders.

Implantable artificial larynxes have now been developed so that patients with throat cancer can speak again. Studies continue on the voice characteristics of artifical larynx users in order to improve the design of the implants and the quality of the sounds they produce.

3. Research Training and Career Development

A shortage of physician investigators remains in the clinical fields of neurosurgery, neurology, neuropathology, neuroepidemiology, neuroimmunology, otolaryngology, otopathology, audiology and speech pathology. The Institute will give special emphasis to the research training of physicians in these areas for research careers in order to ensure continuing advances in the critical area of clinical investigation.

In the Research Career Program, the goals of the Clinical Investigator Development Award (CIDA) are relevant and important. Maintenance of a "critical mass" of clinical investigators needs continuing emphasis and funding by the NINCDS. An earlier Teacher Investigator Development Award, the first such research award aimed principally at physicians, provided a productive mechanism for developing a much needed pool of capable investigators. Support will continue for the newer CIDA Program which offers the potential for increasing this cadre of investigators with provision of more flexibility in fitting the award period to the needs of the individual.

National Institute of Neurological and Communicative Disorders and Stroke

Clinical Research

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987 Estimate
Neurological disorders of early life	$12,194,000	$11,716,000	$11,517,000	$11,214,000
Neurological disorders of adult life	9,153,000	8,773,000	8,568,000	8,343,000
Stroke	17,281,000	16,550,000	16,131,000	15,707,000
Epilepsy	15,105,000	14,472,000	14,122,000	13,751,000
Demyelinating disorders	11,824,000	11,337,000	11,083,000	10,792,000
Neuromuscular disorders	5,728,000	5,501,000	5,403,000	5,261,000
Infectious diseases of the central nervous system	2,196,000	2,105,000	2,071,000	2,017,000
Trauma and injury	14,974,000	14,366,000	14,069,000	13,699,000
Tumors	2,187,000	2,096,000	2,051,000	1,997,000
Neuroendocrine & autonomic nervous system	2,051,000	1,989,000	2,000,000	1,947,000
Learning and behavior	2,379,000	2,285,000	2,247,000	2,188,000
Nervous system function	6,420,000	6,227,000	6,271,000	6,107,000
Metabolism and nutrition	575,000	554,000	548,000	534,000
Hearing and equilibrium	23,562,000	22,581,000	22,052,000	21,473,000
Speech and language	14,565,000	13,941,000	13,568,000	13,212,000
Other sensory disorders	5,527,000	5,314,000	5,236,000	5,098,000
Multicategorical research	124,000	67,000	64,000	62,000
Total	145,845,000	139,874,000	137,001,000	133,402,000

National Institute of Neurological and Communicative Disorders and Stroke

Clinical Research

Impact Data	1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987 Estimate
Budget mechanism:				
Research Project Grants				
Number	413	413	403	399
Amount	$95,572,000	$91,838,000	$88,965,000	$88,286,000
Research Centers				
Number	38	38	38	38
Amount	30,150,000	28,853,000	28,853,000	26,371,000
Other Research				
Number	103	98	98	100
Amount	7,166,000	6,802,000	6,802,000	7,010,000
Total, Research Grants				
Number	554	549	539	537
Amount	132,888,000	127,493,000	124,620,000	121,667,000
Training 1/				
Individual awards				
Number	16	15	15	16
Amount	356,000	334,000	334,000	356,000
Institutional awards				
Number	174	166	166	166
Amount	3,711,000	3,546,000	3,546,000	3,550,000
Total, Training				
Number	190	181	181	182
Amount	4,067,000	3,880,000	3,880,000	3,906,000
R & D Contracts				
Number	42	40	40	38
Amount	8,890,000	8,501,000	8,501,000	7,829,000
TOTAL	145,845,000	139,874,000	137,001,000	133,402,000

1/ Numbers are full-time training positions.

National Institute of Neurological and Communicative Disorders and Stroke

Intramural Research Program

1987 Authorization: Indefinite

Budget Authority:

1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987	Increase or decrease
$48,625,000	$46,532,000	$46,532,000 (FTEs: 458)	$47,804,000 (458)	+ $1,272,000 (--)

Purpose and Method of Operation

The mission of the NINCDS Intramural Research Program (IRP) is to conduct basic and clinical research on the structure, function and malfunction of the brain, spinal cord, ear, muscle and related body organs. These substantial efforts range from basic neurobiological research to clinical trials of newly developed medical and surgical therapies. The laboratories and research clinics are located mainly at NIH in Bethesda, Maryland.

The most extensively supported neurosciences disciplines are neurovirology, neuroimmunology, neurophysiology, neurochemistry, neuropharmacology, neurogenetics, neuropathology, neuro-otolaryngology, neuroepidemiology and biometry. Clinical investigation focuses on demyelinating, metabolic, degenerative, convulsive and neoplastic disorders of the nervous system. The program also contributes substantially to the future prevention of the neurological and communicative diseases through the research training given to young clinical and basic research scientists.

Rationale for Budget Request

The 1987 budget request for intramural research is $47,804,000, an increase of $1,272,000 over the 1986 level.

Intramural investigators will continue to pursue a wide variety of promising research leads. These include neurochemistry of brain and nerve metabolism, especially in relation to lipid storage diseases and seizure disorders; immunological approaches for the early and specific diagnosis and treatment of brain tumors; factors regulating neural and related cell development and regeneration; neural control in relation to disorders of voluntary movements; virus and molecular biological approaches to Alzheimer's disease and other degenerations of the central nervous system; the cause and prevention of damage to the brain due to edema (retention of water) following stroke or trauma; and inner ear processes involved in disorders of hearing and balance. Among the most exciting of these advances are the development and clinical research application of brain imaging techniques such as positron emission tomography and magnetic resonance imaging (MRI) and use of recombinant DNA technology in the study of neurogenetic disorders. The development of a hemi-parkinsonian model of Parkinson's disease with unilateral intracarotid injection of MPTP, a compound which specifically destroys an important part (substantia nigra) of the brain, introduces a unique control system for study of brain implants and anti-parkinsonian drug evaluation.

A. Brain Imaging

Positron emission tomography (PET) studies have demonstrated the feasibility of studying the metabolic consequences of neuronal degeneration, cerebral blood flow interruption, and drug action in the human central nervous system. Specific ligands for a number of neuroreceptors will be used for the study of a variety of brain diseases. The non-invasive MRI techniques localize structural brain abnormalities to a degree not possible by previously available methods, particularly in diseases such as multiple sclerosis. These exciting advances will enable much better diagnosis of brain tumors, inflammatory and ischemic lesions, as well as nervous system degeneration.

B. Communicative Disorders

Multidisciplinary studies of inner ear structures and mechanisms, including sensory cells and neurons and their interactions, are providing new knowledge on the poorly understood mechanisms of hearing. Research on the function of the ear will concentrate on studies of how sound waves are conducted to and interpreted by the brain. The role of specific neurotransmitters in auditory nerve and olivocochlear nerve fibers, and the detailed pharmacological and biochemical characterization of these systems will be studied to open new approaches to management of hearing disorders.

C. Clinical Research on Drug Therapy

Research directed towards the development of improved drug therapies for nervous system disorders will continue with special emphasis on multiple sclerosis and orphan drugs for rare disorders. An integrated program of preclinical and clinical investigations will relate the activity of a particular transmitter system to a specific centrally mediated function. Novel pharmacological agents will be evaluated in animal models (including the MPTP model of Parkinson's disease) and in man for their selective ability to modify these systems and thus ameliorate neurologic symptoms. Drugs for the prevention and control of the convulsive disorders, extrapyramidal movement disorders such as Parkinson's disease, Tourette's syndrome, Huntington's chorea, and for Alzheimer's disease will also receive particular attention.

D. Nervous System Structure and Function

Newer techniques and instrumentation such as freeze fracture, video enhancement, and high-voltage electron microscopy techniques will be applied to studies of the structure and function of nerves and the synapses through which they communicate. Use of monoclonal antibodies will help identify and locate molecules crucial to the integrity and function of the nervous system. Quantitative neuroanatomical methods and novel instrumentation techniques will be used to examine features of spinal neuron biology that are relevant to amyotrophic lateral sclerosis and to spinal cord injury.

E. Neurovirology

Studies of slow infectious viruses involve efforts to delineate the chemical nature of such viruses. Laboratory studies will continue to explore various chronic, progressive central nervous system disorders (such as Creutzfeld-Jakob disease) which appear to be caused by transmissible virus-like agents. Research continues on the ability of certain viruses to induce brain tumors and on attempts to modify the growth of these neoplasms. New immunological and genetic techniques to identify progressive multifocal leukoencephalopathy will be developed. Research on multiple sclerosis will attempt to identify antibodies and other proteins as well as viruses involved in abnormalities of myelin formation; these studies may lead to a specific diagnostic test for multiple sclerosis as well as insights into the pathogenesis of the disorder.

F. Acquired Immune Deficiency Syndrome (AIDS)

A number of important observations have been made by this Institute which will be investigated in depth including the mechanism whereby the AIDS virus enters the brain will be examined. Drugs acting on the AIDS virus in the brain will be examined since the virus in that site is relatively protected from circulating antibodies. The correlation between increased level of certain peripheral enzymes or antibodies and antiviral antibodies to the virus will be analyzed as a potential simple assay system.

G. Molecular Genetics

Initiatives in molecular genetics will seek the chemical basis of many neurological diseases with the goal of preventing and treating inherited and acquired diseases of the nervous system. Research projects will continue to examine the molecular events involved in duplication and expression of animal and viral chromosomes to define the regulation and replication of viruses which cause neurological disease. Analysis of the properties of genes coding for enzymes, especially those which metabolize neurotransmitters, will permit their proper regulation, repair, and transfer. Studies of the expression of these genes in lower organisms are directed towards the large scale production of enzymes for clinical studies of enzyme replacement therapy.

H. Enzyme Replacement Therapy

Procedures to modify enzymes by reconstituting them with lipids to improve their delivery to specific sites in the central nervous system are being developed. This may provide a way to ensure more effective therapy for lipid storage disorders such as Gaucher's disease and Tay-Sachs disease. Studies of how cells synthesize enzymes and locate them correctly in cell membranes as well as protect them from degradation will provide an understanding of how to engineer enzymes and improve their effectiveness as therapeutic agents.

I. Nerve Regeneration and Brain Implants

Methods for enabling regeneration of injured neurons and replacement of injured brain cells are being explored. To transplant peripheral neurons, specific immuno-suppressants are being tested. For the central nervous system chemical toxins (MPTP, Kainic acid) are being used to develop models of degenerative diseases. A laboratory is being organized to focus a new IRP initiative in this area of research.

National Institute of Neurological and Communicative Disorders and Stroke

Research Management and Support

1987 Authorization: Indefinite

Budget Authority:

1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987	Increase or decrease
$17,150,000	$16,261,000	$16,261,000	$16,413,000	+ $152,000
		(FTEs: 209)	(209)	(--)

Purpose and Method of Operation

This activity includes the extramural program directors and their staffs who are responsible for the scientific planning, direction, administration, and review and approval functions of their program's research grant, research contract, and research training programs. The Extramural Activities Program staff are responsible for the Institute's overall grants and contracts administration including processing, award and management activities. This activity also supports the immediate Office of the Director, and the staff which assists the Director in management and direction of the Institute's programs. These units include the administration and financial management activities of the Institute as well as program analysis functions and scientific and health reporting.

Rationale for the Budget Request

The 1987 budget request for research management and support is $16,413,000, an increase of $152,000 over the 1986 level.

National Institute of Neurological and Communicative Disorders and Stroke

Detail of Permanent Positions

	1985 Actual	1986 Estimate	1987 Estimate
ES-5	1	1	1
ES-4	15	15	15
ES-3	7	7	7
Subtotal	23	23	23
GS/GM-15	27	27	27
GS/GM-14	41	41	41
GS/GM-13	35	36	36
GS-12	25	25	25
GS-11	42	44	44
GS-10	2	3	3
GS-9	42	44	44
GS-8	7	7	7
GS-7	56	56	56
GS-6	48	48	48
GS-5	35	35	35
GS-4	11	11	11
GS-3	3	3	3
Subtotal	374	380	380
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	22	22	22
Senior Grade	10	10	10
Full Grade	4	4	4
Senior Assistant Grade	3	3	3
Subtotal	40	40	40
Ungraded	116	116	116
Total permanent positions	553	559	559

THURSDAY, MARCH 13, 1986.

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

WITNESSES

DR. LAWRENCE E. SHULMAN, ACTING DIRECTOR

L. EARL LAURENCE, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

DONALD F. CYPHERS, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

Chairman NATCHER. At this time, we will take up the 1987 Budget of the National Institute of Arthritis and Musculoskeletal and Skin Diseases. We have before the Committee Dr. Lawrence E. Shulman, the Acting Director. Dr. Shulman, it is a pleasure to have you back before the Committee again. Before you give us your statement, tell us who you have there at the table with you.

Dr. SHULMAN. Mr. Chairman, thank you very, very much. With me are Mr. L. Earl Laurence, our Executive officer, and Mr. Donald Cyphers, our Financial Management Officer, sir.

Chairman NATCHER. Thank you very much. We are delighted to have all of you. We will be pleased to hear from you at this time, Dr. Shulman.

OPENING REMARKS

Dr. SHULMAN. Mr. Chairman, as you can well appreciate, it is a great privilege and special honor to appear before you and provide testimony for the first time on behalf of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and to share with you some of the research advances and selected scientific opportunities in these fields. Both the Congress and the President recognized the importance of these research areas with the enactment of Public Law 99-159 which established this new Institute devoted to scientific research in the three areas of arthritis, and musculoskeletal and skin diseases. I emphasize these three areas, sir, because in each field there are many different diseases. There are over 100 types of arthritis, even more skin diseases, and numerous orthopaedic conditions. In each field, there are promising research advances. There are some common scientific themes, but in each field there are many different scientific agendas. I am going to discuss a few of these major diseases with you, sir, and then at the end, if I may, I would like to offer a couple of generalizations with respect to research activities of this new Institute.

First we have new direction for research on rheumatoid arthritis, which is a major crippler among rheumatic diseases. For years, scientific research has indicated that rheumatoid arthritis was an autoimmune disease with a predilection for joints; that it was caused by a cascade of immunologic events and there was also a role for mediators of inflammation. There are now two lines of scientific evidence that rheumatoid arthritis may be caused my one or more infectious agents. The first is that we have several microorganisms as candidates for causing rheumatoid arthritis. We have three candidate viruses. As you remember, two years ago we talked about Epstein-Barr virus, last year about this new parvovirus, and this year there is evidence of rubella virus as reported recently in the New England Journal of Medicine. We have a continuing interest in mycoplasma research. In our intramural program, we have some very exciting research where fragments of bacterial cell walls—of common bacteria, such as streptococci—have been shown to be able to induce in animals first an acute and then a chronic arthritis. We have identified the responsible chemical in the cell wall to be a peptidoglycan. Of course, you know about the spectacular discoveries of Lyme arthritis, the disease that was discovered ten years ago in a small town in Connecticut: that it has been shown to be caused by a spirochetal bacteria and that this bacteria, too, can cause first an acute arthritis and then in some, a chronic arthritis resembling rheumatoid arthritis. The second line of evidence is the new model of rheumatoid arthritis that we mentioned briefly to you last year. This new model was discovered in an inbred strain of mice, MRL/1 mice, which regularly develop swollen joints over the period of three to six months of age. In studying what happens during the evolution of the arthritis in this model, it was seen that the earliest lesion was not that of inflammation as we suspected previously, but a proliferation of the lining cells in the synovium, or joint lining. This is followed by beginning damage in the joint, and then only after that does inflammation take place. There is now an intensive search for retroviruses in this animal model.

The second area that we would like to discuss with you is osteoporosis. This disorder, as you know, provides us with an unusual opportunity for prevention. This is a condition of diminished bone mass—thinning of the bones; 20 million Americans have this. It occurs mostly in post-menopausal women and in the elderly. It is responsible for 70 percent of bone fractures in elderly people occurring mainly in the hip, wrist and spine. As you know, in 1984 we held a major NIH consensus conference on preventive and therapeutic issues relating to osteoporosis. This conference generated much up-to-date information and much interest in the public and the professions. We learned that we all build up our bone mass to the age of 35 years of age and, after that, it is all downhill. The bone loss occurs more frequently, more rapidly in women at around the time of the menopause. We also heard for the first time that we had good data that estrogen therapy in menopausal women could impede this bone loss. We heard also that most people, especially the elderly, were not taking in enough calcium, although we need more data on that certainly. We learned also that exercise is important, and that it is gravitational stress exercise that is important. Our astronauts actually lost calcium when they were studied up in space. Therefore walking is better for us than is swimming in terms of preventing the bone loss that leads to osteoporosis. There are several questions that are left, and we also have no treatment. We have prevention, but we have no treatment whatsoever for osteoporosis. Fluoride is being worked on with a large trial, and we will soon have some data on that, but we need to find other ways of stimulating new bone formation. We have identified some bone growth factors. There is a human skeletal growth factor discovered by Dr. Baylink in California. Dr. William Peck has discovered another factor in St. Louis. That prompts me to report to you that just one year ago there was formed a new voluntary health agency devoted to osteoporosis. It is called the National Osteoporosis Foundation. The new President is Dr. Peck, and the new Chairman of the Board is the Honorable Paul Rogers, formerly of this body. This is a very important area in which we need to do some more work.

The third area of emphasis is osteoarthritis. This is the most common form of arthritis affecting some 16 million people. We are beginning to obtain some valuable knowledge about the chemical changes in the cartilage that are taking place in osteoarthritis, and the messengers, such as Interleukin I and Catabolin, which influence the metabolism of the cells in the cartilage. We had a very interesting conference last summer that addressed eight major questions on osteoarthritis. It was chaired by Dr. Henry Mankin of the Massachusetts General Hospital in Boston and Dr. Kenneth Brandt from Indiana. It was very impressive and several new ideas were generated for research on osteoarthritis. There are two misconceptions with respect to osteoarthritis. One is that it is an inevitable consequence of aging. That is not true. The chemical changes in the cartilage in aging—such as less water—are different than the chemical changes that take place in osteoarthritis. The second point is that it is not necessarily caused by wear and tear. Sure, we have Joe Namath's football knees and Wes Unseld's basketball knees. These are examples of traumatic osteoarthritis. On the other hand, perhaps you may have read an article in last Friday's Washington Post which reported on a study of longdistance runners between the ages of 50 and 72. It was found that they had no more frequency of osteoarthritis either by physical examination or by x-ray than what was found in mature non-runners.

Fourthly, Mr. Chairman, we know from the past two or three hearings that you have a special interest in this terribly blistering disease, epidermolysis bullosa, EB. I thought I would try to bring you up to date as to what is going on in this disease. This is a group of painful, disfiguring, disabling, genetic disorders affecting primarily children. It is dreadful. It causes not only disease in the skin, but disease in the mucous membranes of the body as well. We have some very productive research on just where those blisters take place: It is in the basement membrane zone, which is the zone between the outer layer of the skin and the inner layer of the skin. There are five well-described clinical forms of EB and we have pinpointed, by using monoclonal antibodies and new techniques, exactly where the lesions are. In the most severe form, which is the recessive dystrophic form of EB, we have found that there is a defect in anchoring fibrils. There are fibrils that come up through the skin that anchor the outer layer to the inner layer and keep it on; that is where the lesion is. In recent research in the past year, we have identified the chemical nature of those fibrils. They are Type

VII collagen fibrils. We are also establishing at the present time, a registry on epidermolysis bullosa, as requested by this Committee. The announcement for the registry went out on the street last week. Huntington's Disease, as you know, has had a remarkably productive registry; accordingly, we have patterned the epidermolysis bullosa register after the Huntington's Disease registry. I could provide you with more testimony, but our time is up. We were going to talk about lupus, which is another serious disease; and we have a variety of other research opportunities.

However, I would like to end by sharing a couple of generalizations with you. Underlying all this research is vital basic research. Immunologic research is very important to understanding these diseases. Immunogenetics is also important. But perhaps even more important than all of these is basic research on connective tissues: that consists of collagen and the cushioning effects that we get from proteoglycans produced in certain specialized cells. We have identified major collagen defects in osteogenesis imperfecta, another terrible inherited disease, by the basic research that has been done on collagen. A second general objective of this new Institute is to provide the science base so that we can increase our knowledge about the musculoskeletal system, so we can promote musculoskeletal fitness in our population. We need to develop good recommendations about what exercises are good or bad, what nutrition is good or bad, and what hormones are important in regulating this. We hope to achieve, in terms of musculoskeletal fitness, a companion piece to what the National Heart Institute has done for cardiovascular fitness, and we will ask them to be our tutor. That is our verbal testimony, sir. The budget for this new Institute this year is $106,733,000. I will do my best to try to respond to any questions you have.

Chairman NATCHER. Thank you very much, Dr. Shulman.

[Statement follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Statement of the Acting Director
National Institute of Arthritis and Musculoskeletal and Skin Diseases

As the Acting Director of this new Institute, I am honored to be the first to present to you the programs and accomplishments of both our extramural and intramural scientists and grantees. These diseases - arthritis and musculoskeletal and skin diseases - are numerous and diverse. They afflict millions of Americans, young and old, causing pain, deformity, disability, and death; and in the aggregate, they impose a staggering economic burden upon us all.

Until recently, with notable exceptions, little was known about the causes of these diseases. With the advent of modern biomedical research technology and a new cadre of committed investigators, this outlook has changed rapidly. Provocative advances in all aspects of disease have created opportunities for research that may lead to discovery of the cause and cure for many of these diseases. I am pleased to be able to share with you some of these promising leads and innovative therapeutic achievements emerging from this program.

Rheumatoid Arthritis: The Institute is coordinating a comprehensive research strategy to capitalize on the latest findings relating to rheumatoid arthritis (RA), the major crippling disorder among the rheumatic diseases. Investigators are seeking to identify the infectious agent or agents responsible for initiating the disease process. One such candidate, a parvovirus called RA-1, has been provisionally linked with human RA. A major study searching for infectious agents in early arthritis is planned. Researchers are refining our understanding of the genetic predisposition to developing RA; this genetic makeup underlies the abnormal immune response to an infection that leads to destruction of joints in RA. Other recent research findings point to a role for the nervous system, specifically substance P, in promoting joint inflammation.

New methods of therapeutic approaches for treating RA have become more numerous and effective. Methotrexate, previously used to treat cancer and psoriasis, seems particularly promising. For the future, advanced techniques of biotechnology are being applied to restore normal immune function, and to block inflammation and tissue damage in RA. Identification of a specific causative agent for RA will provide the opportunity for development of a vaccine or other preventive approach.

Osteoarthritis: More than 16 million Americans have osteoarthritis, the most widespread form of arthritis. It primarily affects the cartilage of the joint, causing it to fray, wear, ulcerate, and, in extreme cases, to disappear, leaving a bone-on-bone joint. An encouraging finding of recent research is that osteoarthritis is not necessarily caused by aging. Detailed studies have revealed major biochemical differences between aging cartilage and osteoarthritic cartilage. Recent epidemiologic studies have shown that in older populations the prevalence of osteoarthritis does not increase with age. Research has also refuted the simplistic concept that osteoarthritis results necessarily from wear and tear of the joints. Recent research indicates that long-distance runners over 50 years of age have no more osteoarthritis than "mature" non-runners.

Opportunities have now become available for increased productive research on fundamental mechanisms of osteoarthritis. Much is being learned in the field of articular cartilage biochemistry. Substances have been identified that regulate the abnormal behavior of cartilage cells in osteoarthritis. Improved understanding of interrelationships between biochemical and biomechanical changes in causing osteoarthritis present important opportunities to block the disease process at any one of a number of steps. Efforts are also being made to develop artificial cartilage to repair damaged joints.

Systemic Lupus Erythematosus: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease involving several organs of the body. More than 500,000 people in the United States are estimated to have this disease; most are young women. Although its cause is unknown, SLE is considered to be an autoimmune disease, characterized by excessive production of antibodies directed against the body's own tissues. In SLE, autoimmune antibodies have been shown to damage kidneys and other organs, attack brain cells causing convulsions and psychosis, lead to clotting phenomena which cause spontaneous abortions, or cross the placenta and cause heart and skin defects in newborn infants. Using monoclonal antibodies to seek out these destructive antibodies, investigators are uncovering fundamental genetic defects in SLE and facilitating the development of a sensitive test for identifying and monitoring disease activity in SLE.

With improved early diagnosis and more efficient drug therapy, the past several years have witnessed a heartening trend toward improved survival in SLE. Further progress is anticipated through development of innovative forms of therapy by agents which manipulate the immune system.

Lyme Disease: Solving the entire puzzle of Lyme Disease took researchers only some seven years; their success in piecing together the clues provides an excellent illustration of the importance of both basic and clinical research in characterizing a disease. This disease was first identified in 1975 in youngsters as an acute arthritis, followed in some by a chronic, destructive arthritis resembling rheumatoid arthritis. It was preceded in most by spreading skin lesions (erythema chronica migrans). NIAMS-supported investigators discovered in 1978 that the disease is transmitted by a tick; and by 1980 that antibiotics could effectively treat the disease. The cause of Lyme Disease was pinned down when scientists isolated the spirochete (a bacterium) first from the tick and then from patients with Lyme Disease. A blood test for antibodies against the spirochete has been developed. This definitive linkage of a form of arthritis with an infectious agent has served as a major impetus to identify additional forms of arthritis caused by infection.

Osteoporosis: Osteoporosis, a decrease in bone mass, affects as many as 15 to 20 million Americans, especially post-menopausal women and the elderly. Each year, 1.3 million fractures are attributable to osteoporosis, generating an economic burden estimated at $3.8 billion annually. In normal bone remodeling, as new bone is built, existing bone is resorbed continuously. In osteoporosis, an imbalance in this process leads to the production of porous, weakened bone which is highly susceptible to fractures. Two leading causes of osteoporosis are deficiency of estrogen and deficiency of calcium. Research is ongoing to develop the safest and most effective hormone replacement (estrogen and/or progestin) therapy, and the optimal amount and form of calcium for prevention of bone loss and fractures. Adequate levels of vitamin D, and weight-bearing exercises are also beneficial. Basic research on bone metabolism is greatly needed to discover new ways to stimulate new bone formation, and then be able to treat osteoporosis, once it has developed.

Paget's Disease: Paget's Disease is a major medical problem affecting a large number of people, mostly elderly. In Paget's Disease, the cells responsible for bone resorption function abnormally; this results in mechanically weak and misshapened bones. Recent evidence suggests that Paget's is the result of a slow virus infection. Confirmation and isolation of this virus, as well as research on other hypotheses, are necessary to develop specific therapeutic and prophylactic measures for this disorder. In the meantime, recent studies of treatment with calcitonin and diphosphonates have been very encouraging.

Osteogenesis Imperfecta: Osteogenesis imperfecta is a genetic disease that causes fragile bones leading to fractures in infants and children. Estimated to affect 30,000 people in the U.S., it is the most common heritable disorder of connective tissues. In severe cases, bone fractures may occur even in the fetus. In spectacular research employing the techniques of modern molecular biology, investigators have identified several specific defects in the genetic coding of collagen, the major structural protein of connective tissues.

Low Back Pain: Impairments of the spine are the most common cause of limitation of activity among persons 17 to 45 years of age. Low back pain affects 50 to 80 percent of adults in the U.S. Its total economic impact exceeds $10 billion annually. Both the etiology of low back pain and its optimal treatment are uncertain. The complexity of the back's anatomic supporting structures and nerve pathways have made research on low back pain difficult. The Institute intends to bring together multidisciplinary research teams with expertise in bones, nerves, discs, and muscles to construct research plans directed to this important problem.

Exercise Physiology: With increased national interest in exercise and physical fitness, NIAMS is promoting research on characterizing the responses of muscles, tendons, and ligaments to various forms of exercise and physical training. These basic studies will produce knowledge valuable for the development of optimal rehabilitative programs and the design of more efficient training programs for athletes and others interested in musculoskeletal fitness. This program will aim to define types of exercise which are helpful or harmful for muscles, bone, and other supporting tissues.

Joint Replacements: These operations, usually of the hip, knee, and fingers, are effective in relieving pain and improving joint function, and are reported to have a success rate as high as 90 percent 10 years after implantation. This success rate and the durability of the replacement joints are expected to improve as a result of changes being developed and implemented in the way joints are designed, manufactured, and implanted.

Epidermolysis Bullosa: Epidermolysis bullosa (EB) is a group of tragic, painful, disfiguring and disabling genetic disorders occurring in children. EB causes the skin and other surfaces, including the mucous membranes of the gastrointestinal and respiratory tracts, to blister and become denuded, raw, and scarred. In many cases, the disease resembles a severe burn. As many as 20 forms of EB have been described; some are fatal early in childhood, and many are severely disabling. Newly developed techniques are providing highly important information on the basement membrane zone, the specific region of the skin where the pathology of EB is located, and on new methods to establish an accurate diagnosis of this and related diseases. Research has associated EB with mutations which produce an abnormality in collagenase, the enzyme that breaks down collagen. This fundamental understanding of the disease process has led investigators to treat EB patients with the drug phenytoin (or Dilantin), which blocks the action of collagenase. Dilantin reduces blistering in more than half of patients with EB. NIAMS is making vigorous efforts to strengthen research on EB.

Contact dermatitis: Contact dermatitis is the most common of the immunologic diseases affecting the skin. It comprises the largest single cause of industrial and occupational diseases. Recently, the cellular and immunologic bases for these allergic phenomena have become better understood. Application of this new knowledge may provide the means of impeding their induction.

Vitiligo: Vitiligo, stark white patches of skin, is a poorly understood disease which can cause severe cosmetic disfigurement, serious psychological stress, and interfere with employment, especially in dark-pigmented persons. Thought to be caused by an autoimmune process which destroys an individual's own pigment cells, the disease is characterized by irregular colorless areas of skin. Exploration of this autoimmune hypothesis may create opportunities for blocking the disease process.

Pemphigus vulgaris: Pemphigus vulgaris is a terrible blistering disease that previously carried a high mortality. Autoantibodies directed against skin components have been discovered in high titer in the serum of patients with pemphigus. Recently, it has been clearly established that these antibodies actually cause the blisters of pemphigus to form. Treatment with cortisone-like or other immunosuppressive drugs have made this otherwise dangerous disease more manageable and has been life-saving.

As we move to establish this new institute, we will work together to develop a comprehensive strategy to quicken the pace and productivity of our efforts. This plan will place heavy emphasis on exploiting the benefits of the most sophisticated techniques of molecular biology, immunology, cell biology, and genetics. It will provide for training the next generation of research scientists, and attracting established investigators to these fields. Teams of investigators will be assembled to conduct multidisciplinary research on the most elusive problems we face in arthritis and musculoskeletal and skin diseases. Attempts will be made to strengthen the resources we already support. Finally, the Institute will work to improve accessibility--by researchers, health practitioners, and the public alike--to the results of our basic, clinical, and epidemiologic research.

Mr. Chairman, the 1987 budget request for this Institute is $106,733,000. I will be happy to answer any questions.

SHULMAN, DR. LAWRENCE E.
Acting Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health

July 25, 1919. Boston, Massachusetts

Education: Harvard University, A.B., 1941; Yale University Graduate School, Ph.D., 1945; Yale University School of Medicine, M.D., 1949.

Professional History: 1949-50, Intern, Medicine, The Johns Hopkins Hospital, Baltimore, Maryland. 1950-51, Ayerst, McKenna and Harrison Fellow in Endocrinology, The Johns Hopkins University School of Medicine. 1951-52, Vernon D. Lynch Fellow in Internal Medicine, The Johns Hopkins University School of Medicine. 1952-53, Assistant Resident, The Johns Hopkins Hospital. 1954-present, Physician, The Johns Hopkins Hospital. 1955-75, Director, Connective Tissue Division, Department of Medicine, The Johns Hopkins University School of Medicine. 1960-66, Physician-in-Charge, Arthritis Clinic, The Johns Hopkins Hospital. 1956-67, Physician-in-Charge, Connective Tissue Clinic, The Johns Hopkins Hospital. 1966-69, Physician-in-Chief, Division of Chronic and Community Medicine, The Baltimore City Hospitals, Baltimore, Maryland. 1970-73, Associate Professor of Medical Care and Hospitals, The Johns Hopkins University School of Hygiene and Public Health. 1964-present, Associate Professor of Medicine, The Johns Hopkins University School of Medicine. 1976-80, Acting Associate Director for Arthritis, Musculoskeletal, and Skin Diseases, National Institute of Arthritis, Metabolism, and Digestive Diseases. 1980-83, Associate Director, Arthritis, Musculoskeletal and Skin Diseases, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. 1983-1986, Director, Division of Arthritis, Musculoskeletal, and Skin Diseases, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. 1986-present, Acting Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Professional Organizations: American Association for the Advancement of Science, American College of Physicians, American Federation for Clinical Research, American Rheumatism Association (President, 1974-75), American Society for Bone and Mineral Research, The Arthritis Foundation, Brazilian Society of Rheumatology, Carla Curzio Neapolitan Society, Lupus Foundation of America, New York Academy of Science, Pan American League Against Rheumatism (President, 1982-86), Society for Clinical Trials, Society for Investigative Dermatology, Sydenham Society, United Scleroderma Foundation.

Honors, Awards: Senior Investigator Award, The Arthritis Foundation, 1957-62. Pemberton Memorial Lecture, 1963. Fellow, American College of Physicians, 1967. The Heberden Medal for Research in The Rheumatic Diseases, Heberden Society, London, 1975. Distinguished Service Award, The Arthritis Foundation, 1979. Honorary Member, Brazilian Society of Rheumatology, 1980. Honorary Member, Australian Rheumatism Association, 1985. The Public Health Service Superior Service Award, 1985.

CREATION OF NIAMSD

Chairman **Natcher**. Now, Doctor, you have appeared before our Committee on many occasions. Today we want to welcome you to the Committee in your new role as the Acting Director of this new Institute. Your Institute, as you well know, was created by the Health Research Extension Act, Public Law 99-158. The President vetoed this legislation or similar legislation on two occasions. The second veto was overridden, overwhelmingly, in both the House and the Senate. Has the new Institute been established officially?

Dr. **Shulman**. The new Institute is in the process of being established. It has not finally been established and announced through the Federal Register, but that should come any day now, I understand. Is that right, Dr. Wyngaarden?

Dr. **Wyngaarden**. Yes.

Chairman **Natcher**. As of today, then, you are operating as a separate Institute, but to a certain extent you are still operating in the old Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases; operating with the same staff, I believe, up to this time Is that correct?

Dr. **Shulman**. Yes, sir.

DR. LIPSETT

Chairman **Natcher**. At this point, I would like to mention in the record how sorry we were to hear of the death of Dr. Mortimer Lipsett who died of cancer on November the 10th. Dr. Lipsett was the Director of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. As you well know, he also served as Director of the National Institute of Child Health and Human Development, and as a Director of the NIH Clinical Center. Dr. Lipsett appeared before our Committee on many occasions. We had the highest respect for him. He was a very distinguished scientist and administrator. We on this Committee, like you, Dr. Shulman, and your associates, are sorry to hear of his death, an untimely death and the loss of a great man. You know, when we lose a man at the age of 64, you just cannot understand it. He was a great man. I did want to say this in the record. It was always a pleasure to have him before the Committee. As Dr. Wyngaarden has heard me say on more than one occasion, you are not only unusual people, Dr. Wyngaarden, but able, too. We appreciate the appearance of all you people before our Committee.

PUBLIC LAW 99-158

Now, Dr. Shulman, are any new programs authorized or mandated by Public Law 99-158 as far as your Institute is concerned?

Dr. **Shulman**. You are asking for what are some of the specifics with respect to this?

Chairman **Natcher**. Are there any new programs authorized? Just what is the situation?

Dr. **Shulman**. I would be glad to run over the specific provisions, sir.

Chairman **Natcher**. Yes.

Dr. **Shulman**. Many of the things that are to be accomplished obviously will have to await the appointment of a permanent Director. That is planned to occur as early as possible, during this current fiscal year. The first provision that is important is that there shall be a National Arthritis and Musculoskeletal Diseases plan, and that plan shall be developed by the new Director. It is intended to expand, intensify and coordinate research in several areas. The activities of this Institute are to coordinate with those of other Institutes and shall provide for investigation of all forms of arthritis and musculoskeletal diseases, including sports-related medicine; be concerned with epidemiology, etiology and prevention, primarily, sir, through basic research in areas of immunology, genetics, biochemistry, microbiology and physiology, and bioengineering. This plan shall also include research on the development, trial and evaluation of techniques, drugs and devices; and the refinement, development and evaluation of various devices. It is to establish mechanisms for inquiry in terms of athletic injuries. Therefore, this new plan will be developed with the help of advisory groups by the new Director when he is appointed. In addition, there are expansions of all previously-existing activities. For example, in data systems there was previously, under the National Arthritis Act of 1974 passed on January 4, 1975, an Arthritis Data System. Now there shall be a National Arthritis, and Musculoskeletal and Skin Diseases Data System. We have an Arthritis Information Clearinghouse. That shall now be expanded to include musculoskeletal and skin diseases in addition to arthritis. There are two interagency coordinating committees. There is now an Arthritis Coordinating Committee—that shall become an Arthritis and Musculoskeletal Diseases Coordinating Committee—and a Skin Diseases Coordinating Committee would be formed. We already have an *ad hoc* skin diseases interagency coordinating committee that could provide the basis for the new official committee. There are to be some demonstration projects, as previously, but no resources were ever specifically provided for them. We are now to include musculoskeletal diseases in the name of the Multipurpose Arthritis Centers. For the National Arthritis Advisory Board, a new advisory board is to be created with representatives from the three different fields; it is to be constituted as other advisory boards for other Institutes. These are the essentials. The only other feature that is of importance to the new Institute is a separate section, Section 5 in the Act, on research on lupus erythematosus, which establishes a coordinating committee and a report, and is to be chaired by the Director of the new Institute, sir. Those are the provisions.

Chairman **Natcher**. Thank you, Dr. Shulman. Now, if you will, insert in the record at this point a summary of the provisions of Public Law 99-158 affecting your Institute.

[Information follows:]

PROVISIONS OF P. L. 99-158
(THE HEALTH RESEARCH EXTENSION ACT OF 1985)
AFFECTING
NATIONAL INSTITUTE OF ARTHRITIS AND
MUSCULOSKELETAL AND SKIN DISEASES (NIAMSD)

National Program and Plan for Arthritis and Musculoskeletal Diseases

- Director, NIAMSD, to transmit to Director, NIH, a plan for a national program to expand, intensify, and coordinate activities respecting arthritis and musculoskeletal diseases.

- Plan to be prepared with advice of Advisory Council, with Advisory Board authority to review and evaluate plan's implementation, to periodically update plan, and to include in annual report to Secretary, recommendations (if any) for changes in plan.

- Director to carry out activities of national program in accordance with plan and in coordination with other relevant institutes.

- Director to periodically review, revise, and retransmit plan.

- Plan to address, at least:
  --Epidemiology, etiology, prevention
  --Techniques, drugs, devices
  --Orthopedic replacements or substitutions
  --Means to monitor/prevent athletic injuries

Data System/Clearinghouse

- Current arthritis activities to be expanded to include musculoskeletal and skin dimensions as required by law.

Interagency Coordinating Committees

Secretary shall establish committees for:

1. Arthritis and Musculoskeletal Diseases (this requires expansion of current Arthritis Interagency Coordinating Committee to include musculoskeletal diseases, as required by law).

2. Skin Diseases

Requirements of Committees:

- Reports due to Secretary, NIH Director, NIAMSD Director and Advisory Council 120 days after end of fiscal year.
- Chaired by NIH Director or designee.
- Member agencies: VA, DoD, BID Directors, representatives of all other relevant Federal departments and agencies as determined by Secretary.

Centers: Multipurpose Arthritis and Musculoskeletal

- o Requires expansion of current Multipurpose Arthritis Centers Program
- o Director, consulting with Council, shall provide for...
- o Some changes in legislative description of the Centers.

National Arthritis Advisory Board

- o To address musculoskeletal and skin diseases for the first time, as well as arthritis.
- o To be established within the Institute. Annual report to Secretary.
- o No expiration date or dollar authorization levels.

Lupus Coordinating Committee

- o Secretary shall establish.
- o Director, NIAMSD, to chair.
- o Members: NINCDS, NIAID, NIAMSD, NIGMS, NHLBI, NIDDK, CDC.
- o Purpose: To plan, develop, coordinate, and implement comprehensive Federal initiatives in Lupus Erythematosus research.
- o Report: to Congress within 18 months of law's enactment; nature of projects and expenditures for each.
- o Termination: one month after report rendered.

Biennial Report

- o For inclusion in NIH Director's Biennial Report.

National Advisory Council

- o Secretary shall appoint for each institute.
- o Members (2/3 professionals, 1/3 public)
  - --18 appointed
  - --Ex officio:
    - Secretary
    - NIH Director
    - NIAMSD Director
    - VA Chief Medical Director
    - or Chief Dental Director
    - DoD Assistant Secretary for Health Affairs
    - Other relevant Federal employees

- o Term: 4 years staggered appointments; mandatory 2 year break between 4 year terms.
- o Chairman: Secretary selects from appointment members or may select NIAMSD Director. Two-year term.
- o Reports: Council may include in NIAMSD Director's annual report comments on its activities, progress of institute, and recommendations for future direction and program/policy emphasis. May also prepare other reports.
- o Functions: (1) Advise, assist, consult with, and make recommendations to Secretary and NIAMSD Director; (2) May recommend to Secretary acceptance of conditional gifts; (3) May make recommendations to NIAMSD Director regarding

intramural research.

Research and Training

Director of the Institute shall:

- Carry out research and training programs, including support for training in medical schools, graduate clinical training, graduate training in epidemiology, epidemiology studies, clinical trials, and interdisciplinary research programs.
- Establish programs of evaluation, planning, and dissemination of knowledge related to such research and training.

Demonstration Projects

Director of the Institute may:

- Make grants to public and private nonprofit entities.
- Establish and support projects for the development and demonstration of methods for screening, detection, and referral for treatment of arthritis and musculoskeletal diseases; also, dissemination of information to health and allied health professions.
- Provide for standarization of patient data and recordkeeping for collection, storage, analysis, retrieval, and dissemination of such data in cooperation with these projects, multipurpose arthritis and musculoskeletal diseases centers, and other arthritis and musculoskeletal diseases researchers.

RHEUMATOID ARTHRITIS

Chairman **Natcher**. Under arthritis, Dr. Shulman, in your statement you mentioned rheumatoid arthritis and osteoarthritis. Would you tell us, please, about these?

Dr. **Shulman**. Yes, sir. Be glad to. Rheumatoid arthritis is an inflammatory arthritis. It starts in midlife and affects women a bit more frequently than men. When you see people who are grossly crippled from arthritis, they are more likely to have rheumatoid arthritis. It is the major crippler. The mechanism of disease is clearly quite different from osteoarthritis. The disease in rheumatoid arthritis begins in the joint lining. Rheumatoid arthritis and osteoarthritis have different laboratory findings. There are a whole host of immunological events taking place in rheumatoid arthritis. The treatment is quite different, one from the other. In contrast, osteoarthritis occurs more frequently in the elderly, and in both sexes equally. The disease seems to be primarily in the joint cartilage, although there are other structures in and about the joint that are important. But the main target of the disease initially is in the cartilage and it causes degeneration and fraying of the cartilage. Both of these diseases, I hasten to add, vary greatly in severity. Many people who have osteoarthritis have it mildly; amd many people with rheumatoid arthritis have it mildly. I would think that overall more people with rheumatoid arthritis become disabled. The last figure that I have been told is 58 percent of the people with rheumatoid arthritis are disabled. A much smaller figure would be the case for osteoarthritis. The treatment is entirely different. The treatment of osteoarthritis in terms of drugs is very small. You take either pain medications or first-line anti-inflammatory medications, such as aspirin or its equivalent. Other drug treatments are not indicated for the most part. In rheumatoid arthritis, those who care for patients with rheumatoid arthritis go through a whole series, a cascade, of treatments depending upon the severity: first-line drugs, second-line drugs, third-line drugs. I am happy to report to you that we have some very successful new drugs to treat rheumatoid arthritis, some established and some new upon the scene for which we don't have the final answers yet.

Chairman **Natcher**. Dr. Shulman, can you give us any idea as to the number of people suffering at this time from rheumatoid arthritis and osteoarthritis?

Dr. **Shulman**. Yes, Mr. Chairman. The number of people with rheumatoid arthritis is estimated, according to one survey or another, at a range of from 3 to 7 million people in the United States. The figure that the Arthritis Foundation has been using for osteoarthritis is 16 million people in the United States.

Chairman **Natcher**. Thank you, Doctor. Mr. Conte?

ARTHRITIS AND RELATED RESEARCH

Mr. **Conte**. Thank you, Mr. Chairman. Dr. Shulman, you have been before the Committee a number of times before, but this is your sole appearance in charge of the new Arthritis Institute. I think that is one of the few that I have not been in.

I think one of the main reasons for establishing an Arthritis Institute, which was voted for by the Congress overwhelmingly, over a veto, is the sense that given the number of people affected by arthritis and related disorders, the resources being developed have been devoted to the research needed, which is something of an impetus, shall we say a shot in the arm. What is your perception about the adequacy of the resources being provided to the arthritis and related research?

Dr. SHULMAN. We share with you that there is generally productive research going on in various types of arthritis. We can also say that there has been increasing research on arthritis supported by the NIH. Last year, you remember that Dr. Lipsett's testimony said that over the past decade there was an increase of 86 percent. There are four divisions in the parent Institute of NIADDK. The growth over the decade was greater in the arthritis, musculoskeletal and skin diseases (AMS) division—that is 186 percent of that which it was ten years ago—compared to 173, 150 and 166 for the other three divisions; but it has been the fastest-growing division. That is especially true over the past five years. When funds were allocated within the NIADDK, the quality of the science was going to determine largely the allocation. When Dr. Salans took charge of the NIADDK Institute, he instituted this policy. Arthritis research has fared well in that competition and it is a sign that it is a healthy enterprise; this is so for all three of the fields in the AMS Division.

Mr. CONTE. Is it possible to say the state of the field is such that additional resources can be put productively to use and they would be likely to result in a faster progress of understanding and treating arthritis?

Dr. SHULMAN. Yes, I think that is true of most fields, and certainly true here.

Mr. CONTE. Yes?

Dr. SHULMAN. Yes.

BUDGET FOR NEW INSTITUTE

Mr. CONTE. How does the size of the budget proposed for the Arthritis Institute compare with the size of the budget for the former arthritis division under the National Institutes?

Dr. SHULMAN. It is comparable, sir. What was done in preparing for this hearing and in constructing the budget, the allocation of resources between the two Institutes was done on the basis of the most recent level of scientific activity of the Arthritis, Musculoskeletal and Skin Diseases Division vis-a-vis the other components.

Mr. CONTE. What is the size of your intramural program? Do you have a good amount of activity going on in the intramural program?

Dr. SHULMAN. Yes, sir. The 1985 actual was $6,478,000; the President's Budget is $6,181,000. We have two outstanding organizations that have been transferred from the parent Institute. One is the Arthritis and Rheumatism Branch, where we have several major projects going on, and the other is the Laboratory of Physical Biology where we have some extraordinarily sophisticated muscle biology research going on.

Mr. CONTE. What are your estimates of the additional cost to man the structure required by the separate Institute you have?

Dr. SHULMAN. As testified previously, the estimates have been \$3½ to \$4 million, sir.

Mr. CONTE. Are you planning on building a new building out there?

Dr. WYNGAARDEN. Not at present, Mr. Conte. We have assigned to the new Institute all of the space that they presently occupy that is identifiable with that activity, but we do not have a building program in mind at present.

ARTHROSCOPIC RESEARCH

Mr. CONTE. Do you think you have a role to play in assuring the transfer of the latest technology to the field in the practice of orthopaedics and rheumatology; in such a field as arthroscopy, for instance?

Dr. SHULMAN. Well, this is a very active field. I was just down at the meetings of the Orthopaedic Research Society and the American Academy of Orthopaedic Surgeons in New Orleans. There is very productive research. It is a growing enterprise. You should have seen some of the scientific sessions there that were devoted to biotechnology and improved biomechanical techniques. It is really extraordinary.

Mr. CONTE. Did you see any new technologies in these particular areas?

Dr. SHULMAN. Well, I did not see a major new technology, but I am sure there were some, and I would be glad to provide them for the record if you would like sir.

[Information follows:]

RECENT TECHNOLOGIES IN ORTHOPEDICS

BONE AND JOINT TRANSPLANTATION

Large segments of bone and bone with the joint surface intact are now being transplanted from cadaver bone specimens with great success. The preservation techniques, size compatibility and histocompatibility are much improved over previous methods. Immune system suppressors, such as cyclosporin A_1 are being studied as methods to prevent rejection of the transplanted bone segments. In transplanting portions of ribs or non-weight bearing bones to bone defects in the same individual, the most important advance is the use of microvascular surgery to replace the bone blood supply.

ARTHROSCOPIC SURGERY

Many joint injuries, especially to the knees, threaten the return to active participation in a sport or activity. In a relatively minor surgical procedure, the interior condition of the joints can be evaluated through small needle holes and fiber optic tubes. Now surgery can be performed through this same instrumentation. This surgery can be performed on an out-patient basis under local anesthesia; this is both a great convenience and cost saving for the patient. Cartilage tears can be repaired and tissue debris removed from the joint to aid in healing. Damage to the meniscus can be repaired by sewing loose fragments back to the joint capsule. These latest advances allow replacement of torn ligaments through the arthroscope; this is a much simpler procedure than the complete opening of the joint as required in previous surgical approaches. Arthroscopy is also performed for shoulder, ankle and elbow diagnosis and repair.

KNEE SIMULATOR

Mr. CONTE. I am working with Dr. Ellison in my district, maybe you have heard of him. He came up with this idea of setting up a simulator for the knees. It was pretty similar to the simulators that we have in Oklahoma City for airplane pilots. He really has me intrigued.

Dr. **Shulman**. He has us intrigued, sir. He did come down to see us. I also saw him in New Orleans, as well, and he plans to come back to see us. He has very intriguing new ideas. We will work with him in every way we possibly can.

Mr. **Conte**. I am pleased to hear that. It sounds like a real promising thing.

Dr. **Shulman**. Yes, sir.

INFECTIOUS AGENTS IN ARTHRITIS

Mr. **Conte**. To move into the research area, your statement and the justifications seem to speak pretty definitively about the involvement of some sort of an infectious agent, such as a virus, in rheumatoid arthritis. Is that a fair statement I am making?

Dr. **Shulman**. We have hopes that we will find a virus or other agent definitely proven to be a cause of rheumatoid arthritis. Yes, there are some very interesting new leads, sir. To reiterate, those new viruses are EB virus (the virus of infectious mononucleosis which produces so many different diseases), parvovirus, which causes many of the diseases in animals and has been recently shown to cause disease in humans, and most recently rubella virus. We are also looking for retroviruses. Retroviruses have been shown to cause arthritis in goats; therefore, this is another lead as well.

Mr. **Conte**. Is it the infectious agent itself that causes the symptom, or is it the immune system reaction that then causes some sort of autoimmune reaction that leads to the symptoms?

Dr. **Shulman**. One would think that the best scenario, sir, would be that some infectious agent—and perhaps it is not just one infectious agent, it could be one or more infectious agents—could turn on the system and then lead to immunologic events, which then cause the inflammation.

KNEE JOINT REPLACEMENTS

Mr. **Conte**. Getting off of that for a moment, what can you tell us about the latest development in the replacement of knee joints? Can you give us your latest list of where you think the most significant elements in this area are taking place?

Dr. **Shulman**. Well, there are several new technological developments in knee replacements. At the meetings of the American Academy of Orthopaedic Surgeons, if you went down to see the exhibit sections, you saw several different designs of knee replacements. The new developments are as follows: One is that they used to have a knee replacement that was available, that was the same for both knees. Now they have a knee replacement that acts more like the natural movement; it has a larger flange on the lateral part of the hinge joint itself. Another development is in the use of porous metal. One of the problems with any type of joint replacements, as we discussed previously, is loosening of the acrylic cement that is used to imbed the knee replacement. We now have some understanding as to how that takes place. We have good figures for the hip and that is that after ten years 10 percent of the people have major loosening of that hip replacement. The figures are about the same for the knee. There has been an attempt to develop a mechanism in which you do not use cement: you design it in such a way that new bone grows into the porous metal.

Mr. CONTE. Has that been developed?

Dr. SHULMAN. That is developing.

Mr. CONTE. In other words, it has not been used yet.

Dr. SHULMAN. Yes, it has been used. It is now being widely tested. I cannot, however, give you any good figures as to the comparative efficacy or safety of the new porous material vis-a-vis the old cemented material because enough time has not gone by with the new porous material.

Mr. CONTE. I was talking with an orthopedic doctor in a clinic a couple of weeks ago and he said that with the old type knee with cement he was having 95 percent success after ten years, which is very encouraging.

Dr. SHULMAN. That is great.

Mr. CONTE. The old cement did not hold more than seven years. You would not have any knees with you, would you?

Dr. SHULMAN. Yes, sir. [Laughter.]

I am glad you asked.

Dr. WYNGAARDEN. He has his own and artificial ones. [Laughter.] Which do you want to see, Mr. Conte?

Dr. SHULMAN. Mr. Conte, I am just an arthritis doctor; I am not one of those talented orthopedic surgeons. I will show it to you quickly now, and then perhaps after the hearing you might wish to see more of it. This is the older one, sir; the one for either knee. This is the part that goes down into the lower leg bone, the tibia, here, and this is the part that goes up into the thigh bone, the femur. It fits on there like that if I can show that to you, like this, rocks back and forth. This part here fits under the patella, the knee cap. The next one, sir, is the new development.

Mr. CONTE. This is the one with the bone?

Dr. SHULMAN. This is the porous metallic material, right.

Mr. CONTE. Porous material.

Dr. SHULMAN. This is a new design, and this goes like so. This is the left knee replacement, it is bigger there on the lateral side, and this is the attachment for the knee cap. You can see this porous material. I will show it to you. [Pause.] This is the material into which the bone grows. [Pause.]

Mr. CONTE. Thank you, Mr. Chairman.

Chairman NATCHER. Mr. Early, I yield to you.

CREATION OF NIAMSD

Mr. EARLY. Thank you, Mr. Chairman. Dr. Shulman, we are pleased to see you as the Acting Director and I wish you well. It is so important that this Institute get off to a good start, and I am pleased to see a good person there. Doctor, I understand the implementation will be in three phases. Would you tell us where you are now with regard to the three phases?

Dr. SHULMAN. Yes. The Institute, as you have heard, is being established officially any time now. The Institute has already started to be created in terms of the new appropriation for which we are here today. It is obviously on the road for FY 1987. As we indicated, the new Institute will consist of all the staff and the activities of the previous division of Arthritis and Musculoskeletal and Skin Diseases, and related laboratories from our intramural program. The remaining programs, of course, would be called the NIDDKD. We are going to be called NIAMSD. The three phases will take place as follows: Phase one will occur in this fiscal year when there will be a designation of the Institute and permanent directors for both Institutes will be selected. During this phase, we are getting together and organizing and establishing two advisory councils—one for NIAMSD and the other for NIDDKD—to review our grants during the next year.

Mr. EARLY. Do we need more advisory councils, Doctor?

Dr. SHULMAN. This is the regular advisory council that officially acts as a second-line peer review for our grants. It is a very important body. So this is not an advisory board. This is to be established by law.

Mr. EARLY. Why do we have a peer review and then have someone else check on the peer review? That seems to be a repetition; it really does not seem to be effective.

Dr. SHULMAN. Well, the council acts as a second-line peer review to some degree on the quality of the work, but it does more. It is also concerned with larger questions as to whether or not a field, a scientific area or a disease needs to have special attention. We get broad advice from our advisory councils that we don't get from specific study sections.

Dr. WYNGAARDEN. If I can add to that, I think we are required by statute now to have both levels: the first scientific review for scientific quality and technical feasibility, and the second by the council of the potential funding Institute. By law, we may only fund such projects as are recommended for approval by the council. So we must have both.

Mr. EARLY. I don't know, by law. I think you have to leave the independence with these people. I think that is repetition. It is like we have screening committees and study committees. We should be able to get a new Director within a shorter period of time than we have been doing. We have to protect our own backside all the time and we don't get there.

Dr. WYNGAARDEN. Yes.

Dr. SHULMAN. Did you want me to go on with the second phase?

Mr. EARLY. No, that is all right. I was only concerned with the first phase.

Dr. SHULMAN. Thank you.

Mr. EARLY. How much of the 1987 budget will be for administrative costs?

Dr. SHULMAN. The budget for administrative costs will be $2,953,000, sir.

Mr. EARLY. For the record, show how this compares to other Institutes of comparable size.

Dr. SHULMAN. Yes, we will.

Mr. EARLY. Also for the record, do you plan to make any major changes in policy?

Dr. SHULMAN. We will, sir.

[Information follows:]

COMPARISON OF ADMINISTRATIVE COSTS FOR SMALL INSTITUTES IN 1987

[Dollars in thousands]

	National Institute of Arthritis and Musculoskeletal and Skin Diseases	National Institute on Aging	National Eye Institute	National Institute of Dental Research	National Institute of Environmental Health Sciences
Total budget	$106,733	$145,829	$179,201	$96,482	$187,995
Research management and support	2,953	8,172	6,050	6,741	5,805

ADMINISTRATIVE EMPHASES IN THE NEW NIAMSD INSTITUTE

Administrative policies within the new National Institute of Arthritis and Musculoskeletal and Skin Diseases will be much the same as those of the former AMS division of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. However, there will be changes in emphases, in accordance with and to be responsive to the specific provisions in the language of Pub. L. 99-158, the Health Research Extension Act of 1985. The existing data system, clearinghouse and national advisory board will each be expanded to encompass all three principal programs of the NIAMSD. The current Interagency Coordinating Committee on Arthritis will be expanded to include Musculoskeletal Diseases. A new Interagency Committee on Skin Diseases will be established.

PREPARATION OF 1987 BUDGET

Mr. **EARLY**. Doctor, did you put together the budget that was submitted to Dr. Wyngaarden?

Dr. **SHULMAN**. That budget was submitted on behalf of the parent Institute, the NIADDK, in May.

Mr. **EARLY**. How much was it?

Dr. **SHULMAN**. I have it right here. It was $706,132,000.

Chairman **NATCHER**. Dr. Wyngaarden.

Dr. **WYNGAARDEN**. We divided it because we are separating the two budgets this year.

Mr. **EARLY**. Is that $700 million?

Dr. **WYNGAARDEN**. That would have been the budget for the original total Institute. We put that together before the new law was passed.

Mr. **EARLY**. Do you have a number, Doctor, for this new Institute?

Dr. **SHULMAN**. We have a breakdown subsequent to that. We did not submit it then; no, sir.

Mr. **EARLY**. Dr. Wyngaarden, do you have the number?

Dr. **WYNGAARDEN**. The number submitted was $706 million. Once we cleaved the Institute into the two components, we went back and reallocated the partial budgets. The partial budget for the Arthritis Institute was $146,385.

Mr. **EARLY**. From you to OMB?

Dr. **WYNGAARDEN**. From the Department to OMB, it was $126,298,000.

Mr. **EARLY**. Thank you. Doctor, I have a lot of reservations. I think the Institutes are losing their independence. I don't think it is good for research, I don't think it is good for science, I don't think it is good for anything; and you identified the perfect example for me. I was so pleased that you singled out epidermolysis bullosa. You know, that is a disease—speaking only for myself on this Committee—that only got attention because several families came and showed their children. It was so sad. They did not have enough of a constituency—thank God—to have had any political muscle. In my opinion, those are the ones that are going to fall through the cracks unless you people have some independence. That was just tremendous. The people who had their children here did not look to be rich people. They did not have a lobbyist or anything else. Now, is your Institute able to address that? With this specific budget, I don't think we will ever get to those types of things, Dr. Shulman. Would you comment as far as little diseases like that? If you are making all these reductions, are some of them going to fall through the cracks?

Dr. **SHULMAN**. We have been working with the budgets we have now, and have been sort of productive. I appreciate your concern. All I could really say is that we will do the best we can with what resources we have.

EPIDERMOLYSIS BULLOSA

Mr. **EARLY**. It is for us to make sure you have the resources. I don't want to embarrass the Chairman, but he was the one that zeroed in on it. We did not earmark or target. He was the one that put in the money for epidermolysis bullosa, or we would not have gotten there. Now you identify where it is; you suggest that it might be on a registry similar to Huntington's Disease. Does that indicate that you are going to be able to locate the marker? You have, in your comments, been able to locate it as to whether it is within the outer or the inner skin; but do you expect to be able to identify the gene?

Dr. **SHULMAN**. There is active research going on right now, Mr. Early, by Dr. Eugene Bauer at Washington University, St. Louis, in which he is trying to look for the gene for collagenase that may be the source of this disease. So there is very active research going on?

Mr. **EARLY**. How is he funded?

Dr. **SHULMAN**. A research grant.

Mr. **EARLY**. Would you, for the record, supply what the length of his grant is; what type of reductions he is going to have to take this specific year? And, also, the program's name because I am certainly very impressed with the Institute being able to do that. I recall last year, Dr. Shulman, the parents of these children really chastised me, out in the hall, for not doing it. I appreciate their fight and we should never be satisfied. I just think that if we don't keep funding at legitimate levels and leave the independent people there, we won't get to epidermolysis bullosa and pemphigus vulgaris. They are going to fall through the cracks. We will stay with arthritis and diabetes and cancer because they are political.

[Information follows:]

EB AND COLLAGENASE RESEARCH

The National Institute of Arthritis and Musculoskeletal and Skin Diseases is currently supporting, through its Skin Diseases Program, some important research studies by Dr. Eugene Bauer of Washington University in St. Louis. He is characterizing the stimulatory effects of various cytokines on colleagenase enzyme expression in cultured fibroblast skin cells. He is also defining the ontogeny of collagenase active in human skin at various stages of development. These studies by Dr. Bauer on collagenase should provide valuable information on collagenase's role in Epidermolysis Bullosa and other diseases of connective tissue.

These studies are supported through a research project grant which is in it tenth year in 1986. The committed total costs were approximately $189,000, and the awarded total costs were approximately $183,000. We expect Dr. Bauer to submit an application to recomplete for a new project period beginning in 1987.

OSTEOARTHRITIS

Mr. **Early**. Doctor, on osteoarthritis, recent epidemiological studies have shown that in older populations the prevalence of osteoarthritis does not increase with age?

Dr. **Shulman**. Yes, this was a study carried out in one of our centers. It showed that if you study an elderly population to see whether the frequency of osteoarthritis increases linearly with increasing age, it does not do that.

Mr. **Early**. It does not. Is that something that is new?

Dr. **Shulman**. When I used to practice rheumatology at the Johns Hopkins before joining the NIH, I used to teach with this little story. The story is of the 80-year-old man who came to his physician with a swollen right knee. He was examined by the physician, obtaining a thorough work-up: x-rays, laboratory tests. On returning a week later the patient said, "Well, what is the story, Doctor?" The doctor replied, "Well, you have osteoarthritis." "What kind of arthritis is that?" He said, "Well, that is the kind of arthritis you get when you get older." The patient said to the doctor, "Why, that is funny, Doctor, my left knee is just as old as my right."

Mr. **Early**. Pretty good observation. [Laughter.]

INFECTIOUS AGENTS IN ARTHRITIS

Doctor, what is the latest thinking on the role of infectious agents in arthritis?

Dr. **Shulman**. We are encouraged by the evidence. We know that we have infectious agents in arthritis. We know that streptococci, staphylococci, all types of ordinary bacteria cause arthritis. We also know that Lyme arthritis, as I mentioned in my opening statement, is an outstanding example of how a known infection can cause arthritis. However Dr. Steere, the discoverer of Lyme arthritis, still does not know how the infectious agent actually causes the arthritis. He is studying this intensively at the moment, and we hope to learn a great deal from that.

Mr. **Early**. Are there plans for research in this area?

Dr. **Shulman**. Yes, sir.

Mr. **Early**. Is there money to do it?

Dr. **Shulman**. He is continuing his research, sir.

Mr. **Early**. Is it expanding any other places?

Dr. **Shulman**. There is some in other institutions research, but Yale is the center of research on Lyme arthritis because the investigators at Yale have a large captive population with which to study this disease. Are you asking about the whole rheumatoid arthritis field?

Mr. **Early**. Right.

Dr. **Shulman**. Oh, yes, we have a lot of research going on in rheumatoid arthritis. We also have research looking for klebsiella bacteria in spinal arthritis that affects young men especially.

Mr. **Early**. Are you going to have to curtail any of that because of this budget?

Dr. **Shulman**. We will be continuing the level of activity.

Mr. **Early**. Are you going to slow it down because of this budget?

Dr. **Shulman**. I think that if the resources are constrained, there will be less growth; that is about all I could say.

Mr. **Early**. Then you are slowing it down.

Dr. **Shulman**. We still have a lot of good research going on, sir.

OSTEOARTHRITIS

Mr. **Early**. It is not stopping, but it is going to slow down. Doctor, what research do you currently support on the treatment of osteoarthritis?

Dr. **Shulman**. In the treatment of osteoarthritis, we have a clinical trial that is just being launched. It is a multi-center clinical trial, which will evaluate whether pain-killing medicines are as effective as are anti-inflammatory medicines. We have all these anti-inflammatory medicines, such as Motrin and Naproxen other newer agents that have appeared upon the market. The study is designed to determine whether or not anti-inflammatory therapy has any advantage over painkilling therapy in osteoarthritis.

Mr. **Early**. Doctor, you say you have a multi-center clinical trial. Is that one that has been appropriated?

Dr. **Shulman**. Yes, sir.

Mr. **Early**. When do you expect to start on that?

Dr. **Shulman**. The trial will be starting this summer.

Mr. **Early**. Would you, for the record, tell us about when you are going to complete it?

Dr. **Shulman**. We will.

Mr. **Early**. And if any reductions you are going to make in your budget will delay it.

Dr. **Shulman**. Yes, sir.

Mr. **Early**. If it is going to delay it, I would like to know for how long.

[Information follows:]

CLINICAL TRIAL ON OSTEOARTHRITIS

The National Institute of Arthritis and Musculoskeletal and Skin Diseases is supporting a new clinical trial to compare the efficacy of anti-inflammatory and painkilling medicines in the treatment of osteoarthritis. This study is being directed by Dr. John Ward at the University of Utah, together with two other arthritis clinical studies under a new NIAMSD research contract. The osteoarthritis trial will begin in July 1986. It is expected that all patients will be entered into the study by September of 1987. Each patient will participate in the study for a two year period. Thus, we expect to complete all the data-gathering of the clinical trial by September of 1989. This study has been provided full funding this year, and will be fully funded in 1987.

SPECIALIZED CENTERS OF RESEARCH

Mr. **Early**. What is your professional opinion of using specialized research centers as a funding mechanism?

Dr. **Shulman**. This whole question of Specialized Centers for Research has been discussed in depth by leaders in the field of arthritis and musculoskeletal diseases. A great deal of attention has been paid to it. It has been discussed with our Institute's Advisory Council favorably, been discussed with the National Arthritis Advisory Board whose last two annual reports have come out strongly in favor of them. They are patterned after the Specialized Centers for Research in the National Heart, Lung and Blood Institute, which have had a 15-year history with such centers and they have been judged to be extraordinarily productive. We talked with the leaders of the Heart, Lung and Blood Institute who have a strong opinion that specialized centers are a very valuable adjunct to their total research portfolio. They allow concentrated coordinated basic and clinical research focussed on disease areas of great national importance.

Mr. **Early**. Would you place in the record your own professional opinion as to whether you think it speeds up the process of achieving the solutions.

Dr. **Shulman**. Okay. Thank you.

Mr. **Early**. Thank you, Mr. Chairman.

[Information follows:]

THE ROLE OF SCORS IN FACILITATING HEALTH RESEARCH

We have assessed the scientific feasibility and potential benefits of establishing a program of Specialized Centers of Research in arthritis and musculoskeletal diseases. This assessment determines that both the magnitude of the health problems associated with arthritis and musculoskeletal diseases and the unprecedented scientific opportunities in these fields warrant such an initiative and that the SCORs mechanism provide an extremely valuable adjunct to the Institute's research portfolio.

The goal of specialized centers of research in arthritis and musculoskeletal diseases would be to accelerate the pace of research on their causes, progression, and treatment and to expedite the transfer of research results to improved health care. The proposed centers program would focus on rheumatoid arthritis, osteoarthritis, and osteoporosis. These diseases are three of the most debilitating of the more than 100 kinds of arthritis and related disorders, which are estimated to cost the nation over $25 billion a year. As the American population ages, the number of people affected and the economic costs are increasing. The means to reversing these trends is through research.

We have noted great interest on the part of several outstanding investigators in the establishment of SCORs in these fields. If a program of such centers in arthritis and musculoskeletal diseases were initiated, it is expected that the quality of applications would be high and the competition vigorous. Such an action by the Institute has been strongly supported for years by several professional and voluntary organizations.

Based upon these findings, the NIH is supportive of the establishment of Specialized Centers of Research in arthritis and musculoskeletal diseases, specifically rheumatoid arthritis, osteoarthritis, and osteoporosis, if additional resources were to be made available for this purpose.

HEREDITY AND ARTHRITIS

Chairman **Natcher**. Now, Dr. Shulman, is arthritis hereditary?

Dr. **Shulman**. That prompts me to say there are different types of arthritis, once again, sir. It is a theme that we have throughout this testimony. There are different types of heredity factors in different types of arthritis. I will briefly discuss that. In rheumatoid arthritis, there is a tissue type, called DRw-4, that is associated with the disease. Rheumatoid arthritis tends to occur in families, but not greatly so. In another type of arthritis, ankylosing spondylitis, which is inflammation of the spine, occurring primarily in younger men, the evidence is much greater that you have familial aggregation. Gout, still another type of arthritis, is an example of another inherited genetic disease, one in which Dr. Wyngaarden has made so many contributions. There is also a genetic component to systemic lupus erythematosus. As a matter of fact, there is a recent study using monoclonal antibodies to the idiotype of anti-DNA antibodies, showing a large proportion of a symptomatic relatives of lupus patients having this underlying immunogenetic defect. The first tissue type relating strongly to human disease was in ankylosing spondylitis in 1973 when it was shown that the tissue type HLA-B27 was present in 95 percent of people with ankylosing spondylitis compared to 5 to 7 percent in the general population. In summary, there are several different genetic factors in arthritis, per se.

DIET AND ARTHRITIS

Chairman NATCHER. Doctor, is there any evidence that diet or exercise have any effect on prevention of arthritis?

Dr. SHULMAN. To my knowledge, there are few specific preventive approaches to arthritis in the diet. We have some interesting new evidence about the importance of fish oils as they might relate to development of protection against inflammation. Certain types of fish oils are protective in an experimental model of lupus in inbred strains of mice. If we broaden our definition of arthritis to include osteoporosis, the importance of calcium in preventing bone loss may be a significant preventive factor.

MYCOPLASMAS

Chairman NATCHER. What evidence is there that mycoplasmas are related to rheumatoid arthritis?

Dr. SHULMAN. This very interesting question has been reviewed repeatedly; there has been an interest in this area for well over 20 years, as we both know. Mycoplasmas are small bacteria; they clearly can cause arthritis in experimental animals. We have sent a report to this Committee on this two years ago looking carefully at this particular question. We had the National Arthritis Advisory Board Committee evaluate this whole question; and there is, as yet, no convincing evidence that mycoplasmas can be found in the joint tissues of persons with arthritis.

Chairman NATCHER. Go ahead, Mr. Early.

KNEE JOINT REPLACEMENTS

Mr. EARLY [presiding]. Doctor, are we doing enough knee and hip replacement surgeries now so that we can almost look at them as routine?

Dr. SHULMAN. We are doing many joint replacements, and they are not viewed as being routine. The orthopaedic surgeons believe that these operations are usually done in places where there has been experience doing them. I went around to the exhibit area down at that orthopaedic surgery meeting to take a look at the models that are available in terms of the various techniques. It requires very careful technology; a surgeon needs to be talented and skilled to do that type of operation optimally.

Mr. **EARLY**. I would like to give you my impression of the old knee and the new knee. As a layman, I just thought that you would be in here this year with a much lighter, flexible thing.

Dr. **SHULMAN**. Pretty heavy, is it not?

Mr. **EARLY**. Yes, sure is.

Dr. **SHULMAN**. I have no idea, sir. The weight may help in its stability, however.

Mr. **EARLY**. Well, I don't have enough professionalism to suggest that.

Dr. **SHULMAN**. Neither do I, sir.

SPORTS MEDICINE

Mr. **EARLY**. Doctor, what time do you have for research in sports medicine?

Dr. **SHULMAN**. Sports medicine is an area that needs to be pursued. I have asked Dr. Steven Gordon, our Musculoskeletal Diseases Director, who is here, to identify and consult with the leaders in sports medicine. There are different organizations concerned with sports medicine. I have talked with some of them personally, and I have discussed the question with leaders in orthopaedic surgery. Some interesting work has been carried out, but much more scientific work needs to be done. We are surveying opinions of experts as to what needs to be done and we will be gathering a group together to make appropriate plans.

Mr. **EARLY**. They seem to be making so much progress, Dr. Shulman, with regards to the surgery. Now, you see a football player go in on an outpatient basis and get something done that used to take weeks.

Dr. **SHULMAN**. I agree.

SYSTEMIC LUPUS ERYTHEMATOSUS

Mr. **EARLY**. Fine. Can you report any recent research advances related to lupus?

Dr. **SHULMAN**. Yes, sir.

Mr. **EARLY**. Would you, please?

Dr. **SHULMAN**. This happens to be a field of my own personal professional interest. I did research on lupus for many years before joining the NIH. There is a lot of action in lupus research. We have awarded, in our Institute, over $12.5 million for research devoted to lupus. At the annual scientific meetings of rheumatologists, about 25 percent of the scientific papers are devoted to lupus. Let's get down to some advances. The first of which is published from Boston, from the laboratory of Dr. Robert Schwartz, who has used both monoclonal antibodies, in murine models and human monoclonal antibodies, to show that there is cross-reactivity between anti-DNA and anti-cardiolipin antibodies. Anti-DNA antibodies are at the heart of lupus; they are the ones that are thought to cause the kidney disease of lupus. Immune complexes of DNA and anti-DNA antibodies form in the circulation and go and hit the kidney, and cause the kidney damage. Lupus is considered to be the best example of general autoimmune disease in man.

Mr. **Early**. Why?

Dr. **Shulman**. Because it is a generalized disease and there are lots of antibodies. Patients with lupus produce antibodies, many, many different kinds of antibodies. Some people have described lupus as a disease of serologic schizophrenia or immunologic epilepsy. It is thought to be an autoimmune disease because the antibodies are thought to be directed against the patient's own tissues or chemicals. Now, the interesting thing that Dr. Schwartz and his group found was that there was that cross-reactivity with anticardiolipin antibodies. Cardiolipin is a phospholipid; this phospholipid could be in bacterial cell walls. Therefore, the antigen that will turn on the so-called autoantibody could actually come from outside the body.

Mr. **Early**. I really don't understand the medical terms. Are we getting pretty close to identifying this; can we do anything about it?

Dr. **Shulman**. We have made a lot of progress. I can say that a lot has been accomplished, in the outlook for lupus. When Dr. Wyngaarden and I were in medical school, lupus was thought to be a rare, almost uniformly-fatal disease. An internist was thought to be a genius if he made a diagnosis of lupus. Then we had discoveries of a special lupus blood cell, the LE Cell; we had the discoveries of ACTH and cortisone as effective treatments; and that began to change the whole outlook. In 1955, 30 years ago, the outlook for lupus patients was survivorship 50 percent four years after diagnosis. That is what the figures were at that time. Now, the figures are 95 percent survivorship ten years after diagnosis.

Mr. **Early**. Ten years?

Dr. **Shulman**. Yes, sir. Some people who have lupus can look forward to a full life span. The outlook for lupus has changed tremendously.

Mr. **Early**. What is the money we are spending now going to do for us?

Dr. **Shulman**. We still have people who don't make it. We have a mission to find the key dominant factor in lupus. We have many factors as possible etiologic agents.

Mr. **Early**. Are we spending research money to identify more?

Dr. **Shulman**. We are spending moneys on basic research on lupus. As we said previously, we have $12.5 million of interesting research going on.

Mr. **Early**. Doctor, I tell you it is just too bad that the people who have epidermolysis bullosa couldn't hear the comment you made. I am absolutely convinced that the private sector would have never gotten involved in that—and it was identified several years ago as a significant disease. I mean, your progress on this is certainly appreciated. What significant new research opportunities could be lost as a result of the reductions you have in your request? Are you starting any new clinical trials in 1987?

CLINICAL TRIALS

Dr. **Shulman**. Had we planned any clinical trials?

Mr. EARLY. Yes.

Dr. SHULMAN. Two.

Mr. EARLY. Will this budget allow you to start them?

Dr. SHULMAN. No, sir.

Mr. EARLY. Are you going to have to curtail any clinical trials?

Dr. SHULMAN. No, sir.

Mr. EARLY. Will they be carried to fruition at the same rate, Doctor?

Dr. SHULMAN. I think that we will be proceeding with most of the clinical trials. Some of them, if they are on a grant basis, will take the same degree of negotiated reductions as others. Those that we are supporting by contract, will continue as planned.

Mr. EARLY. Thank you, Doctor.

Chairman NATCHER. Dr. Shulman, I want to thank you and your associates for appearing before us on behalf of your budget request for the fiscal year 1987. Doctor, this has been a good hearing and we appreciate your appearance.

Dr. SHULMAN. Thank you, Mr. Chairman.

Chairman NATCHER. We are in recess.

[The following questions were submitted to be answered for the record:]

MYCOPLASMAS

Mr. Natcher. What evidence is there that mycoplasmas are related to rheumatoid arthritis?

Dr. Shulman. A report on that subject was sent to this Committee two years ago examining that particular question. A committee of the National Arthritis Advisory Board investigated this matter and stated that there is, as yet, no convincing evidence that mycoplasma can be found in humans to be related to arthritis.

In summary, research has demonstrated that some arthritic diseases in animal species are caused by mycoplasmas. The mycoplasmas are consistently found to be present in the affected animals. Similarly conclusive evidence, however, has been lacking in human studies, despite repeated efforts. Many studies carried out with rigorous procedures, have yielded negative results in their search for mycoplasmas in human synovial fluid and tissues.

Mr. Natcher. What evidence is there that antibiotic therapy is an effective treatment for rheumatoid arthritis?

Dr. Shulman. The National Arthritis Advisory Board committee which studied this matter concluded that antibiotic therapy has not yet been demonstrated, through commonly accepted double-blind clinical trial methodology, to be an effective treatment for rheumatoid arthritis.

Mr. Natcher. How much consideration have you given to support of a clinical trial of antibiotic therapy for rheumatoid arthritis?

Dr. Shulman. The Institute has given this subject full consideration and attention. It has encouraged submission of research proposals to test the efficacy of antibiotic therapy for arthritis, both in animal model systems and in humans. One of these applications is currently being reviewed. Another was unfortunately not approved by the NIH's peer review groups for reasons that are remediable. The reasons for disapproval have been communicated to the investigators. We have encouraged revision and resubmission of this latter proposal; and the investigators have indicated their willingness to do so. The Institute has also recently conducted a scientific workshop to address the entire area of an infectious etiology for early arthritis. These groups have stated that it is premature to initiate a clinical trial of antibiotic therapy until it is clear that microorganisms are associated with the disease, or that antibiotics have other potentially therapeutic properties.

Mr. Natcher. In our report last year we asked you to explore the feasibility of establishing specialized centers of research in arthritis and musculoskeletal diseases. We have your report on this subject. Tell us briefly about your findings and conclusions.

Dr. Shulman. We have assessed the scientific feasibility and potential benefits of establishing a program of Specialized Centers of Research in arthritis and musculoskeletal diseases.

This assessment determined that both the magnitude of the health problems associated with arthritis and musculoskeletal diseases and the unprecedented scientific opportunities in these fields warrant such an initiative and that the SCORs mechanism provide an extremely valuable adjunct to the Institute's research portfolio.

The goal of specialized centers of research in arthritis and musculoskeletal diseases would be to accelerate the pace of research on their causes, progression, and treatment and to expedite the transfer of research results to improved health care. The proposed centers program would focus on rheumatoid arthritis, osteoarthritis, and osteoporosis. These diseases are three of the most debilitating of the more than 100 kinds of arthritis and related disorders, which are estimated to cost the nation over $25 billion a year. As the American population ages, the number of people affected and the economic costs are increasing. The means to reversing these trends is through research.

We have noted great interest on the part of several outstanding investigators in the establishment of SCORs in these fields. If a program of such centers in arthritis and musculoskeletal diseases were initiated, it is expected that the quality of applications would be high and the competition vigorous. Such an action by the Institute has been strongly supported for years by several professional and voluntary organizations.

Based upon these findings, the NIH is supportive of the establishment of Specialized Centers of Research in arthritis and musculoskeletal diseases, specifically rheumatoid arthritis, osteoarthritis, and osteoporosis, subject to the availability of funds.

Mr. Natcher. Do you have any plans to start any such centers in the forseeable future?

Dr. Shulman. While such centers have been recommended by staff, Advisory Councils, and the National Arthritis Advisory Board, this FY 1987 budget does not provide for Specialized Centers of Research.

Mr. Natcher. How do you feel, in general, about funding centers as opposed to investigator-initiated research grants?

Dr. Shulman. We believe that both research programs are very important. They provide different mechanisms and approaches for gaining new knowledge about these diseases; and both contribute to a complementary research portfolio.

PSORIASIS

Mr. Natcher. This is a skin disease which afflicts many Americans. Can you report any progress in either treatment or prevention of this disease?

Dr. Shulman. With respect to treatment of psoriasis, a major advance in the last few years was the development of PUVA, (a tanning agent, psoralen, combined with ultraviolet radiation).

Patients in an institute-supported multicentered trial are still undergoing long term follow-up for long term sequelae. The significance and incidence of these long term sequelae will ultimately determine just how useful PUVA is in treatment of psoriasis. Among more recently developed treatments, there has been interest in several derivatives of retinoids for their utility in the treatment of psoriasis, either by themselves or in combination with PUVA. As for prevention of psoriasis, there has been little progress to report to you.

Mr. Conte. Dr. Wyngaarden, I know there is a search on for permanent Director of the new Institute, and I certainly think Dr. Shulman is a good man. But I saw the advertisement in the New England Journal of Medicine the other day, and there was one thing that puzzled me. One of the mandatory qualifications was research experience of research programs in one or more areas related to diabetes, digestive and kidney disorders. Why would you be asking for a Director of the Arthritis Institute with his or her research qualifications in diabetes, digestive and kidney disorders?

Dr. Shulman. I would like to answer that question on Dr. Wyngaarden's behalf. Obviously, the new Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases should have expertise in arthritis and musculoskeletal and skin disorders, and not in diabetes, digestive and kidney disorders. The latter wording, though clearly incorrect, somehow made its way into the journal announcement when advertisements for that Director as well as for the Director of the National Institute of Diabetes and Digestive and Kidney Diseases were being prepared.

Mr. Conte. Is there any relationship between stress and the severity of arthritis or the onset of arthritic episodes, and are you sponsoring any research in this and other behavioral research?

Dr. Shulman. To my knowledge there is no proven relationship between stress in the initiation of arthritis. There is some behavioral research in a few projects in the arthritis centers.

Mr. Conte. In your justification, it states that NIAMSD intends to encourage additional fundamental studies in exercise physiology and patho-physiology, including research on muscles, tendons and ligaments. It further states that the Institute will promote much needed further research on sports injuries. What kinds of further research on sports injuries would you say is much needed?

Dr. Shulman. A significant problem in sports medicine is an insufficient scientific basis for some of the recommended approaches to training, treatment of injuries, and rehabilitation. A major long-term goal of the NIAMSD will be to establish a foundation of strong science and scientists on which to formulate future clinical research directions. One example would be an assessment of surgical and rehabilitative approaches to clinical management of torn anterior cruciate ligaments.

Staff of the Musculoskeletal Diseases Program are studying several alternatives for enhancing the research effort in sports medicine science. Interviews with individual scientists, representatives of various research groups, and private practitioners (trainers, physical therapists, surgeons, etc.) will help in developing plans for this important field.

Mr. Conte. How does the number of new and competing grants in the budget for FY 1987 compare with the number of new and competing grants for the arthritis division over the past couple of years?

Dr. Shulman. Our request for FY 1987 will provide for 148 new and competing continuation research project grants. This compares to 173 which we expect to fund in FY 1986, and past year levels for the division of 190 in FY 1985 and 172 in FY 1984.

Mr. Conte. Tell us a little about your centers program and whether it should include specialized centers in rheumatoid arthritis and osteoarthritis.

Dr. Shulman. The Multipurpose Arthritis Centers Program (MACs) currently consists of 13 centers, distributed nationally, performing basic and/or clinical biomedical research, educational research, and community demonstrations/health services research. The Principal Investigator of each MAC defines the scientific emphasis for the center's research activities which are diverse within each center and vary greatly from center to center.

Specialized Centers of Research (SCORs), on the other hand, were recommended as an addition to our centers program by both staff and the National Arthritis Advisory Board, because it would enable groups of investigators to concentrate and focus on a coordinated basic and clinical research program on major diseases of national importance, such as rheumatoid arthritis, osteoarthritis, and osteopsoriasis. These recommendations for SCORs are based and patterned after the highly successful SCORs sponsored and funded by the Heart Institute (NHLBI) in hypertension, myocardial infarction and other major diseases of national importance.

Mr. Conte. Last year, you mentioned irradiation of joints as a possible new treatment of rheumatoid arthritis. This year, I believe I saw one of your statements indicating that there were some potential side effects. What kinds of problems are you finding with this treatment?

Dr. Shulman. The true efficacy and safety of radiation synovectomy will be based on experiences with a larger patient population observed over longer periods of time. The ideal radionuclide is still being sought that will produce the desired synovectomy without any damage to normal articular cartilage or damage to remote tissues. Extra-articular leakage from the joint is considered to be at a safe level but further limits are being sought. Thermographic scanning procedures are currently being evaluated as a means of assessing the effectiveness of the therapy in persons with arthritis, as well as the value of nuclear magnetic resonance imaging.

Mr. Conte. With regard to osteoarthritis, your statement indicates research findings that it is not necessarily caused by aging, but that studies have shown major biological differences between aging cartilage and osteoarthritic cartilage. What kinds of differences are you finding?

Dr. Shulman. The differences being found are in the biochemical constituents of cartilage with relative amounts or established normal ratios being changed in opposite directions when aging normal cartilage is compared with osteoarthritic cartilage. For example, with aging, water content decreases, keratan sulfate increases, and chondroitin-4-sulfate decreases. In contrast, in osteoarthritis, water content increases, keratan sulfate decreases, and chondroitin-4-sulfate increases as well.

Mr. Conte. Your statement also indicates your view that opportunities have now become available for increased productive research on fundamental mechanisms of osteoarthritis. What kinds of opportunities?

Dr. Shulman. Mr. Conte, our scientists engaging in osteoarthritis research have learned more on specific biochemical changes of cartilage, and the influences of biomechanical forces on the cartilage. They have also discovered new substances, such as catabolin or interleukin-1, produced by joint membranes or other sources, that regulate the metabolism and pathology of osteoarthritic cartilage. This past July, we had a major scientific workshop addressing eight vital questions about osteoarthritis; the workshop proved highly productive, generating more than 90 specific recommendations for future research on osteoarthritis.

OSTEOPOROSIS

Mr. Roybal. As public concern over osteoporosis has grown, the consumption of nutrient supplements has increased markedly. What efforts has the Institute made to educate medical practitioners and the public on what has been learned about these supplements?

Dr. Shulman. In April 1984, the NIH held a Consensus Conference on Osteoporosis, which generated considerably increased interest on osteoporosis and its prevention in both the public and the medical profession. It made certain recommendations concerning calcium and Vitamin D intake, among others, as determined by a panel of experts who had reviewed written materials and scientific publications at the conference. The conference's findings were published in the Journal of the American Medical Association and cited broadly in the press. The panel recommended levels of calcium intake for certain ages and according to sex. It stated that this requirement could be met by diet alone, or if this were not practical, by supplementary calcium pills or capsules. New information concerning calcium requirements, and the optimal form and timing of supplements is appearing. This subject will be reviewed again at a workshop on osteoporosis to be convened in FY 1987; and the findings therefrom will be widely and promptly disseminated. Further awards in this area may be needed.

Mr. Roybal. How have or will the basic research on bone metabolism and the clinical studies on osteoporosis, including further studies on hormone replacement and nutrient supplements, be affected by the current budget proposals, in terms of the number of projects and the funding in 1985, 1986, and 1987? What effect will the budget proposals have on the development of effective treatment for a disease which currently costs us almost $4 billion a year?

Dr. Shulman. In FY 1985, the Institute supported 35 projects in osteoporosis research for a total of $4,424,000. In FY 1986, we expect to spent $4,895,000, and in FY 1987, $4,760,000 for research concerned with osteoporosis. Current budget proposals may slow the overall pace of research a bit, but we are quite confident that investigators will proceed firmly in their quests for new knowledge concerning, and effect treatments for, osteoporosis.

TRANSFER OF RESEARCH FINDINGS INTO COMMUNITY PRACTICE

Mr. Roybal. What type of activities will the Institute be undertaking to improve the accessibility to the public and medical providers of what has been learned through the Institute's research? What level of funding was devoted to these types of activities in 1985 and is projected for 1986 (post-sequestration) and 1987? How would additional funds best be spent in this area and what benefits might be expected from this additional expenditure? What special efforts, if any, have been made to reach providers who serve large numbers of elderly patients?

Dr. Shulman. The research findings of the Institute have been and will continue to be made available to the public and to providers through a number of avenues. First, the scientific literature detailing both basic and clinical findings is widely disseminated and read. In addition, the Institute funds the

Arthritis Information Clearinghouse which provides information about the research, care, and treatment of rheumatic diseases to health professionals across the country. This clearinghouse will be expanded in the new Institute to include information about musculoskeletal and skin diseases as well. Many of the health professionals reached by the Arthritis Information Clearinghouse care for the elderly population afflicted with various forms of the rheumatic diseases. Funding for the Clearinghouse in FY 1985 was $279,788, and is estimated to be $295,000 in FY 1986 and $285,000 in FY 1987.

The Institute's Information Office also is involved with disseminating information to the public through press releases, brochures, and pamphlets. In addition, this office cooperates closely with several voluntary health organizations who are active in communicating at a lay level timely information about current research supported by NIAMSD. Recent published examples of these efforts include Living with Epidermolysis Bullosa, Understanding Paget's Disease, What you Should know About Vitiligo, and Osteoporosis: Cause, Treatment and Prevention.

ARTHRITIS CENTERS

Mr. Roybal. Please list the name and location of the Multipurpose Arthritis Centers and the level of program funding for 1985, 1986 (post-sequestration), and 1987.

Dr. Shulman. I am pleased to provide you with the following list of centers. The levels of funding for those centers not yet awarded in 1986 and those anticipated for 1987 are shown as estimates.

NIAMSD Research Centers

(Dollars in thousands)

Principal Investigator	Grantee Institution	1985 Actual	1986 Estimate	1987 Request
Dr. Giles Bole	Univ. Michigan, Ann Arbor	$897	$572	---*
Dr. Kenneth Brandt	Indiana Univ., Indianapolis	355	---*	---
Dr. Halsted Holman	Stanford Univ.	755	671	---*
Dr. Alan Cohen	Boston Univ.	1,163	842 est	---*
Dr. William Koopman	Alabama Univ.	827	755	---*
Dr. Ira Goldstein	Univ. California, San Francisco	593	433	$410 est
Dr. Naomi Rothfield	Univ. Connecticut	247**	882	840 est
Dr. Gordon Sharp	Univ. Missouri	851	595 est	---*
Dr. Roland Moskowitz	Case Western Reserve, Cleveland	934	930	885 est
Dr. John Winfield	Univ. North Carolina, Chapel Hill	785	692 est	660 est
Dr. Frank Schmid	Northwestern Univ.	705	472	---*
Dr. Norman Talal	Univ. Texas, San Antonio	540	502 est	480 est
Dr. Matthew Liang	Brigham & Women's Hosp., Boston	1,044	899	---*
Competing Research Centers Estimate			1,162	5,677
Budgeted Total		9,696	9,407	8,952

* Competing for possible renewal.
** Partial year funding only.

Mr. Stokes. The FY 1987 request for your Institute in $116.733 million. What important research activities will be postponed as a result of this budget?

Dr. Shulman. Actually, Mr. Stokes, the 1987 request will provide quite adequately for most of our ongoing research, a number of important new initiatives have been considered and other new opportunities have become apparent which cannot be pursued within the available resources.

1. Osteoporosis - Osteoporosis affects 15-20 million persons, mostly postmenopausal women and elderly persons; and is the major underlying cause of bone fractures. Recommendations from an NIH Consensus Development Conference on Osteoporosis in 1984 and a planning meeting of expert scientists in 1985 call for increased research projects on hormone replacements, calcium intake, optimal exercise, improved methods to measure bone mass, and basic bone metabolism to implement improved prevention programs and develop new methods to promote new bone formation. An initiative in research project grants could cost approximately $1,400,000.
2. Search for Infectious Agents in Early Arthritis - In major rheumatic diseases, such as rheumatoid arthritis, recent research provides important evidence implicating several specific microorganisms as primary initiating causes in an immunocompromised host. There is special interest, with respect to rheumatoid arthritis, in mycoplasma, rubella virus and parvovirus. New biomedical technologies have been developed for identifying these microorganisms in joint tissues. A recent successful workshop has formulated a detailed agenda for this research, which is estimated to cost $810,000.

3. Cause of Osteoarthritis - Osteoarthritis is the most common form of arthritis, affecting some 16 million Americans. On July 21-25, 1985, a major workshop was held to identify and focus on the many possible causative pathways of osteoarthritis. This productive workshop generated more than 90 specific research recommendations for implementation, which would cost $1,100,000 to implement.

4. Low Back Pain - Spinal impairments constitute the most common cause of disability in persons 17-45 years of age, with an economic impact on the nation of $10 billion annually. A workshop is planned to encourage much needed research on low back pain; multidisciplinary research would receive special emphasis. These projects would cost $675,000.

5. Allergic and Irritant Contact Dermatitis - Recent new research on immunological events and inflammation in the skin provides unusual opportunities to determine the causes of primary irritant and allergic contact dermatitis, and to discover new effective therapies for this major industrial disease. To pursue these opportunities would cost an estimated $1,100,000.

6. Specialized Centers of Research (SCORs) in Arthritis and Musculoskeletal Diseases - These Centers are designed to concentrate research efforts on high priority rheumatic diseases of national importance. The research is integrated: both basic

science and clinical research components are mandated. The National Arthritis Advisory Board has recommended for the past two years that such Centers (SCORs) be established in osteoarthritis, rheumatoid arthritis and osteoporosis - each a major problem with a minimum (a critical mass) of three Centers for each disease. Establishment of 9 SCORs is estimated to cost $7,700,000.

7. Research Career Awards - NIAMSD has a substantial shortfall in the research career award category so that hardly any new research career awards can be made in FY 1986 and FY 1987. In addition, current institutional Physician Scientist Awards will be capped at five positions rather than the ten originally planned. This is particularly devastating since the NIAMSD has a substantial commitment to basic research and the training of MD basic researchers. To add 15 more individual and institutional slots would cost $750,000.

8. Clinical Trial on Epidermolysis Bullosa: Efficacy of Dilantin and Treatment of Esophageal Strictures. The efficacy of dilantin for treatment of the skin lesions of epidermolysis bullosa (EB) would be tested in a randomized, double-blind, placebo-controlled, crossover study. Another part of this study would be a prospective longitudinal follow-up of patients with EB esophageal strictures who had been treated with bouginage or colonic transposition. Contract support is envisioned, at an estimated cost of $500,000.

9. Clinical Trial on Efficacy of 13-cis Retinoic Acid in Treating Keratinizing Disorders. The efficacy of 13-cis retinoic acid in the treatment of ichthyosis and other keratinizing disorders would be assessed with a multicentered, randomized, double-blind, placebo-controlled crossover trial. The cooperative agreement mechanism would be used, with support for all the centers totaling $1,000,000.

Mr. Stokes. How is your institute responding to the directive in the 1986 Senate report that a high priority be given to lupus research? What groups are considered at high risk for this disease?

Dr. Shulman. Research on lupus erythematosus (SLE), Mr. Stokes, continues at a high and productive level. Funding for lupus research in FY 1985 by our Institute was $12,625,000. It is now estimated that certain specific antibodies (anti-Ro) can induce a widespread rash in lupus patients and abnormal heart rhythm in newborn infants, whereas others, such as anti-neuronal antibodies, are responsible for the convulsions and/or psychoses. In other patients using new monoclonal antibody technologies, our researchers have raised the possibility of a causal agent in the environment, have identified a new underlying genetic defect and have developed innovative therapeutic approaches in experimental models of lupus. Our intramural scientists have developed still another new effective treatment for active lupus nephritis.

The vast majority, approximately 90 percent, of lupus patients are young women whose disease begins in adolescence or in young adult life. Lupus is three times more common in black women than in white women. In addition, according to recent studies, it seems to be unusually common in Chinese women.

Mr. Stokes. As you know, I am interested in research on vitiligo, a disease which affects all races, but particularly blacks. What is the status of funding for the vitiligo consortium group?

Dr. Shulman. The vitiligo program project (several research projects carried out by a consortium of investigators at Yale, Howard, Massachusetts, and Cincinnati Universities) was considered to be meritorious and has been once again awarded funding for three years beginning April 1, 1986.

Mr. Stokes. I would like to know whether the vitiligo center grant was renewed for three years. If so, what is the rationale for reducing the funding period from five to three years?

Dr. Shulman. The vitiligo center grant was renewed for three years, rather than five years, on the recommendation of the initial expert review group because of scientific issues and considerations. This application contained four individual project proposals, one of which described a project lasting only three years. Two of the other projects, although offered by established investigators, involved ventures into areas at which they had not yet proven their skills. The reviewers felt that such proposals, though meritorious, should be re-examined after a project period of three years. For these reasons, the entire program project was recommended by the reviewers for approval for three years. Both the Institute staff and its National Advisory Council reviewed this question of length of funding in great detail and concurred unanimously with the recommendations of the initial review group.

Mr. Stokes. Arthritis and related bone diseases affect more than 40 million Americans. How do minorities fare with regard to the incidence of arthritis?

Dr. Shulman. The following is a brief summary of some of the generally accepted sex, race and age risk factors for major categories of arthritis and musculoskeletal diseases.

1. Osteoporosis: There is a higher incidence in women as compared to men (8:1 for spinal fracture and 2:1 for hip fracture). The incidence is higher in white women than in black women.

2. Osteoarthritis: In women there is a higher incidence of osteoarthritis in the hands. For other joints of the body no clear sex difference exists. No clear incidence difference exists between blacks and whites. Osteoarthritis generally increases with age. In men the increase occurs earlier and levels off, while in women the condition starts later and continues to progress.

3. Rheumatoid Arthritis: Women are affected more often, approximately twice, than men. There is a low incidence in Asians.

4. Ankylosing Spondylitis: This disorder occurs much more commonly in men than women. It is rare in African Blacks and Japanese. It usually starts at 15-35 years of age.

5. Lupus: Lupus currently afflicts approximately 500,000 people in the United States. It affects minority women disproportionally to the rest of the population. Blacks have three-fold higher incidence, prevalence, and mortality rates of lupus than do whites. People of oriental origin, and possibly, people of Hispanic origin, may also have an increased risk for developing lupus. In all groups, the disease is far more prevalent in women than men, in a ratio of 9:1.

6. Low Back Pain: The incidence of symptoms is about the same in men and women. Men have considerably higher disability compensation than women. No racial differences seem to exist.

7. Scoliosis: Women have a slightly greater incidence of small lateral curves of the spine; however, in the curves that progress to severe levels and require clinical intervention, women have a 5:1 greater incidence than men. No racial differences seem to exist. This condition starts in childhood or adolescence.

Mr. Stokes. What progress is being made in preventing the occurrence of arthritis?

Dr. Shulman. The intense study, ongoing, to determine early events associated with initiation of disease that undoubtedly occur before its clinical manifestation will provide the best clues to prevention. The means for making the earliest possible diagnosis are highly desirable and a better understanding of the events that immediately precede it may lead to the possibility of interrupting the sequence of events at some point or identifying important factors associated with the earliest onset of the disease.

Mr. Stokes. What is the status of the Multipurpose Arthritis Centers in the 1986 revised and 1987 budgets?

Dr. Shulman. The Multipurpose Arthritis Centers will continue to be funded during both fiscal years 1986 and 1987. Thirteen such centers will be provided funding during each fiscal year at a level of $9,407,000 for FY 1986 and $8,952,000 for FY 1987.

Mr. Stokes. What areas of research conducted by the Centers will be affected by the reduced levels of support?

Dr. Shulman. The Institute is planning to reduce the funding for each Multipurpose Arthritis Center by an average of 13 percent. Each Center Director and his/her staff will decide how best to accommodate to the reduced funding. Since centers devote a high proportion of their funding to personnel costs, some center projects may have to be eliminated or amended.

Mr. Stokes. What is your Institute doing to increase the number of minorities supported through institutional training grants that go to nonminority institutions?

Dr. Shulman. We are currently preparing new guidelines for investigators who are preparing an institutional training grant application. The applicant will be required to include a description of 1) specific plans for recruitment of minorities, and 2) the past record of the institution in the selection of minorities. Subsequent review of the application at NIH will include an assessment of the institution's activities regarding minority training.

Mr. Stokes. Do you establish goals for your senior administrators for addressing minority program and personnel issues? If not, why not?

Dr. Shulman. The Institute has made equal employment opportunity and affirmative action goals an essential element of the performance appraisal of each of its senior administrators.

Mr. Stokes. How do you hold your senior officers accountable for meeting those goals?

Dr. Shulman. The work performance of every senior administrator in the Institute is reviewed annually to evaluate whether the employee's performance has met the goals set forth at the beginning of the appraisal period. This evaluation becomes part of the official personnel record of each senior administrator.

Mr. Stokes. For the record, please supply the following information for SES, senior level administrative, and senior level professional positions in your Institute: the current number of all such positions and the current number of these positions occupied by blacks.

Dr. Shulman. Of 27 Senior Executive Service, senior level administrative and senior level professional staff, we currently have no Blacks. Despite significant efforts, we have had little success in recruiting Black M.D.'s and Ph.D.'s for these positions.

Mr. Stokes. An increase of $908 thousand is requested in FY 1987 for research management and support for the second stage of establishing the new Institute. Specifically, how will these funds be spent?

Dr. Shulman. These funds will be used to establish in part the necessary administrative structure to form an independently operating Institute. This will include forming the Office of the Director, and to establish an Office of Program Planning and Evaluation, a Budget Office, and then an Office of Extramural Activities. In 1987 the new NIAMSD will support the review activities of a newly formed National Advisory Council. We intend to continue to share with the parent (NIDDKD) Institute during 1987 the essential services of grants management, contracts management, review, personnel and public information. Some additional costs will also result as we seek to fulfill our newly authorized activities: expansion of our data system, clearinghouse and national advisory board to encompass all three principal programs of the NIAMSD; expansion of our current Interagency Coordinating Committee on Arthritis to include Musculoskeletal Diseases; and establishment of a new Interagency Coordinating Committee in the area of Skin Diseases.

Mr. Early. Will the budget constraints in both FY86 and FY87 effect the establishment of the Institute and the hiring of new staff?

Dr. Shulman. The Institute is being established and a permanent Director is being recruited. Once a Director is aboard, the issue of further staff will be discussed. Meanwhile, staff is being shared with the NIDDKD.

Mr. Early. Under the FY86 enacted level, NIAMSD would be able to fund 199 new and competing research grants. Under the Administration's revised FY86 proposal NIAMSD would fund only 173 or 26 fewer? Doctor, would you tell us briefly what areas of research would be affected by this reduction?

Dr. Shulman. Funding priorities are established by determination of the scientific merit of each research grant proposal. The 26 fewer grants will therefore be distributed among the scientific areas of the Institute. Each program will share in this reduction.

Mr. Early. The FY87 budget request would fund 148 new and competing grants, 51 fewer than the FY86 post-sequestration level and 42 less than FY85. What would your payline be under the FY86 revised request?

Dr. Shulman. We estimate that the payline under the FY 1986 revised level will be at a priority score of approximately 150.

Mr. Early. What would it be under the FY87 budget request?

Dr. Shulman. The FY 1987 request is estimated to fund to a priority score of approximately 140.

Mr. Early. What is your estimate for FY86, without the rescission?

Dr. Shulman. A priority score of approximately 160.

Mr. Early. What was your payline in FY85?

Dr. Shulman. 165.

Mr. Early. What percentage of approved grants would be funded under the FY86 revised and the FY87 budget requests? How does this compare to your original FY86 estimate? How does it compare to FY85?

Dr. Shulman. The revised 1986 budget would allow funding of approximately 27.5% of our approved research project grant applications. The 1987 Request would fund about 23% of approvals. The original 1986 budget would have permitted awarding 30% of approvals. In 1985 the Institute funded 34% of approvals.

Mr. Early. According to the budget justification there will be downward negotiations of 12.8% and 13.3% in competing and noncompeting grants, respectively. Will each grant be reduced by these amounts? What impact will reductions of this size have on the Institute's research activities?

Dr. Shulman. These will be the average downward negotiations. Each grant will be looked at individually. Reductions above five or six percent are likely to have a significant impact on the quality and depth of the proposed scientific investigations, and are likely to impair the success of many projects, by reducing research staff, supplies and equipment.

Mr. Early. In your professional judgment, Doctor, do you have any serious concerns about the size of the downward negotiations the project grants are being forced to take under this budget request?

Dr. Shulman. Yes, sir.

Mr. Early. The budget indicates that direct costs for competing research centers will be reduced by 13% in FY86 and 20% in FY87. Are reductions of this size something we need to be concerned about?

Dr. Shulman. Yes, when funding levels are reduced to this degree, research efforts in all areas cannot be sustained at the same level.

Mr. Early. What effect will these cuts have on the research programs at these centers?

Dr. Shulman. These research centers have a greater portion of their funding devoted to personnel costs than do other sorts of research mechanisms. Accordingly, funding for selected professional staff may have to be deleted. As a result, specific approved projects may have to be discontinued to conserve resources and maintain the quality of the research effort.

Mr. Early. How will the reduction in the size and scope of the centers program affect NIAMSD's program plans--both immediate and long range?

Dr. Shulman. The current program of Multipurpose Arthritis Centers, under these circumstances, can be maintained, although the dimensions of their research activities may need to be diminished. The National Institute of Arthritis and Musculoskeletal and Skin Diseases has repeatedly received advice both from its National Advisory Council and from the National Arthritis Advisory Board to implement a program of Specialized Centers of Research in arthritis and musculoskeletal diseases. Moreover, an ad hoc Skin Diseases Advisory Group has recommended a program of Core Centers for skin disease research. A reduction in the size and scope of funding will will prevent establishment of both of these research center programs.

Mr. Early. I understand that 14 research centers are to be supported in FY86 and FY87. How many centers are up for renewal in FY86? For the record provide the names and locations of these centers.

Dr. Shulman. Only one of the Multipurpose Arthritis Centers supported in FY 1985 is competing for FY 1986 funding. That Center is at the University of Indiana at Indianapolis, under the direction of Dr. Kenneth D. Brandt. Two new Center applications are also competing for the single MAC award which is available this year.

Mr. Early. How many Centers will be up for renewal in FY87? Provide the names and locations of these for the record.

Dr. Shulman. In FY 1987, seven existing Multipurpose Arthritis Centers will compete for grant support, together with many other qualified applicants. The seven Centers are:

University of Michigan, Ann Arbor	Dr. Giles Bole
Stanford University, Palo Alto	Dr. Halsted Holman
Boston University, Boston	Dr. Alan Cohen
University of Alabama, Birmingham	Dr. William Koopman
University of Missouri, Columbia	Dr. Gordon Sharp
Northwestern University, Chicago	Dr. Frank Schmid
Brigham & Women's Hospital, Boston	Dr. Matthew Liang

Mr. Early. How many new clinical trials will be started in FY86? What are they?

Dr. Shulman. We are initiating four new clinical trials this year. Three of these are being carried out as multi-centered clinical trials, with the coordinating center at the University of Utah. They are: 1) the efficacy of hydroxychloroquine in the treatment of systemic lupus erythmetosus, 2) a comparison of an analgesic drug with a non-steroidal anti-inflammatory agent in osteoarthritis, and 3) the efficacy of methotrexate and gold compounds combined to be compared with each agent alone in the treatment of rheumatoid arthritis. Fourthly, intramural investigators and the Institute's Arthritis and Rheumatism Branch, collaborating with researchers in the National Cancer Institute, are performing a pilot study of high dose methotrexate chemotherapy for rheumatoid arthritis.

Mr. Early. Doctor, will you have to curtail any ongoing clinical trials with your FY87 budget request? If so, which ones?

Dr. Shulman. No.

Mr. Early. Will you be able to start any new clinical trials in FY87?

Dr. Shulman. No, we will not be initiating any new clinical trials in 1987.

Mr. Early. Are there any high priority clinical trials which are ready but cannot be initiated because of lack of funds in the FY87 request? If so, please provide a list of these, along with a brief description and the associated costs, including first year costs.

Dr. Shulman. There are two clinical trials which we would initiate if funds were available for this purpose.

NATIONAL INSTITUTE OF ARTHRITIS AND
MUSCULOSKELETAL AND SKIN DISEASES

Clinical Trials Which Could Be Initiated
If Funds Were Available

	Estimated Cost ($ in thousands)	
	FY 1987	Total
Epidermolysis Bullosa: Efficacy of Dilantin and Treatment of Esophageal Strictures.	$ 500	$2,500
The efficacy of dilantin for treatment of the skin lesions of epidermolysis bullosa (EB) would be tested in a randomized, double-blind, placebo-controlled, crossover study. Another part of this study would be a prospective longitudinal follow-up of patients with EB esophageal strictures who had been treated with bouginage or colonic transposition. Contract support would be used.		
Efficacy of 13-cis Retinoic Acid in Treating Keratinizing Disorders.	$1,000	$3,000
The efficacy of 13-cis retinoic acid in the treatment of ichthyosis and other keratinizing disorders would be assessed with a multicentered, randomized, double-blind, placebo-controlled crossover trial. The cooperative agreement mechanism would be used.		

Mr. Early. Doctor, is the Institute using the Small Business Innovative Research program? If yes, for the record provide a more detailed explanation.

Dr. Shulman. In 1985 we awarded 10 SBIR grants, totaling $1,231,000. During the current year we expect to award 14 SBIR grants, totaling $1,238,000. Within the 1987 Request we expect to award 8 SBIR grants, totaling $1,147,000. I would like to report to you two exciting projects which we have supported through this program in the field of skin diseases.

We are supporting a phase I SBIR award to develop derivatives of the synthetic vitamin A called Accutane, which is currently used systemically. The derivatives are intended to avoid many of the side effects of the currently available systemic drug by acting through local application. Based upon promising data from this phase I project, the small business firm has received a $1 million pledge from a larger drug manufacturer for final development and marketing of the promising derivatives, following the phase II SBIR study.

The Institute is also supporting the phase II award for an SBIR grantee who is developing tuneable dye lasers with output characteristics which make them useful for treatment of vascular and pigmented lesions of the skin, as well as removal of tattoos. Six lasers have been built, five of which are undergoing experimental use at participating clinics; the sixth has already been sold. Theoretically, these lasers will be superior to other treatments for these conditions.

Mr. Early. Would you give us a few examples of how the Institute utilizes its Research and Development contract mechanism?

Dr. Shulman. The contract mechanism is used chiefly for multi-centered clinical trials. A highly successful endeavour has been a series of clinical studies of rheumatoid diseases conducted at the University of Utah coordinating a consortium of participating clinics across the country. Another example of the use of the contract mechanism is to support a 16 clinic trial of the use of the PUVA (psoralen plus ultraviolet light) treatment for psoriosis. In addition, the Institute has supported a multicenter trial of an experimental therapy for arthritis in children, both in the United States and the USSR, as part of its program of international activities.

Mr. Early. Will the reduction of one R&D contract award in FY87 have a significant impact on your programs?

Dr. Shulman. The 1987 Request provides for continuation of the most essential research and development contracts. We do not feel that loss of one contract will seriously hurt our program.

Mr. Early. What are the latest advances in osteoarthritis research and treatment?

Dr. Shulman. Recent investigational studies have shown that chemical changes in cartilage in osteoarthritis are different from chemical changes in cartilage with aging. Substances such as interleukin-1, produced in the synovial membrane, have been shown to act on the cartilage to produce chemical changes observed in osteoarthritis. Very recently, a marker of cartilage turnover, keratan-sulfate, has been found to be elevated in the blood of patients with osteoarthritis.

Relief of pain and preservation of joint motion are the main objectives of treatment. There are no new agents that can impede the progression of the basic process of cartilage degradation and erosion. Treatment is symptomatic rather than specific. Total joint replacements for hips and knees have considerably enhanced the outlook for many patients who can now maintain independence in their activities of daily living.

Mr. Early. For the record insert a list which compares your total budget and the amounts available for osteoarthritis research for FY85, the FY86 post-sequestration level (without the rescission), and the FY 87 estimates.

Dr. Shulman. The comparison you asked for is as follows:

	NIAMSD Budget	Osteoarthritis Research
1985 Actual	$108,808,000	$3,911,000
1986 Available After Sequestering	$111,312,000	$4,428,000
1987 Request	$106,733,000	$4,531,000

Mr. Early. What is the cost to society for the treatment of osteoarthritis and rheumatoid arthritis?

Dr. Shulman. Osteoarthritis cripples more than 16 million Americans and the number of victims of rheumatoid arthritis is estimated to be 3-7 million. From estimates of the Arthritis Foundation, the economic costs of all rheumatic diseases, wich affect a total of more than 37 million Americans, is over $25 billion annually. Unfortunately, sir, I don't have figures for you on the cost of treatment of osteoarthritis and rheumatoid arthritis.

Mr. Early. The report recently submitted on the feasibility and appropriateness of specialized centers on rheumatoid and osteoarthritis stated that these Centers would be "an important impetus to the national research effort". What do you estimate the cost of establishing a Center would be?

Dr. Shulman. The average cost of a Specialized Center of Research in Arthritis and Musculoskeletal Diseases is estimated to be $855,000, including indirect costs, in FY 1987.

Mr. Early. What would be the optimal number of Centers you would like to establish in the first year of such a program?

Dr. Shulman. We think that for the first year of an optimal program of Specialized Centers of Research, the appropriate minimal number would encompass the three scientific fields of osteoarthritis, rheumatoid arthritis and osteoporosis, with a critical minimal mass of three Centers in each field, for a total of nine centers. These Specialized Centers for Research (SCORs) in the National Heart, Lung, and Blood Institute have had five to ten centers for each disease, (e.g., high blood pressure).

Mr. Early. If an increase over the FY87 request is provided, how would you use these additional funds?

Dr. Shulman. In addition to minimizing the downward negotiations in research grants and research centers, there are great needs in supporting research career awards, research training, intramural research and administrative costs for the new Institute.

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed by lack of funds in the FY87 budget?

Dr. Shulman. With a reduction in our budget, we expect that research initiatives will have to be delayed.

Mr. Early. Please provide for the record a list of these, along with a brief description and the funding requirements associated with each.

Dr. Shulman. Here is the list you requested:

1. Osteoporosis - Osteoporosis affects 15-20 million persons, mostly postmenopausal women and elderly persons, and is the major underlying cause of bone fractures. Recommendations from an NIH Consensus Development Conference on Osteoporosis in 1984 and a planning meeting of expert scientists in 1985 call for increased research projects on hormone replacements, calcium intake, optimal exercise, improved methods to measure bone mass, and basic bone metabolism to implement improved prevention programs and develop new methods to promote new bone formation. An initiative in research project grants would cost approximately $1,400,000.

2. Search for Infectious Agents in Early Arthritis - In major rheumatic diseases, such as rheumatoid arthritis, recent research provides important evidence implicating several specific microorganisms as primary initiating causes in an immunocompromised host. There is special interest, with respect to rheumatoid arthritis, in mycoplasma, rubella virus and parvovirus. New biomedical technologies have been developed for identifying these microorganisms in joint tissues. A recent successful workshop has formulated a detailed agenda for this research, which is estimated to cost $810,000.

3. Cause of Osteoarthritis - Osteoarthritis is the most common form of arthritis, affecting some 16 million Americans. On July 21-25, 1985, a major workshop was held to identify and focus on the many possible causative pathways of osteoarthritis. This productive workshop generated more than 90 specific research recommendations for implementation, which would cost $1,100,000 to implement.

4. Low Back Pain - Spinal impairments constitute the most common cause of disability in persons 17-45 years of age, with an economic impact on the nation of $10 billion annually. A workshop is planned to encourage much needed research on low back pain; multidisciplinary research would receive special emphasis. These projects would cost $675,000.

5. Allergic and Irritant Contact Dermatitis - Recent new research on immunological events and inflammation in the skin provides unusual opportunities to determine the causes of primary irritant and allergic contact dermatitis, and to discover new effective therapies for this major industrial disease. To pursue these opportunities would cost an estimated $1,100,000.

6. Specialized Centers of Research (SCORs) in Arthritis and Musculoskeletal Diseases - These Centers are designed to concentrate research efforts on high priority rheumatic diseases of national importance. The research is integrated: both basic science

and clinical research components are mandated. The National Arthritis Advisory Board has recommended for the past two years that such Centers (SCORs) be established in osteoarthritis, rheumatoid arthritis and osteoporosis - each a major problem - with a minimum (a critical mass) of three Centers for each disease. Establishment of 9 SCORs is estimated to cost $7,700,000.

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8. Clinical Trial on Epidermolysis Bullosa: Efficacy of Dilantin and Treatment of Esophageal Strictures. The efficacy of dilantin for treatment of the skin lesions of epidermolysis bullosa (EB) would be tested in a randomized, double-blind, placebo-controlled, crossover study. Another part of this study would be a prospective longitudinal follow-up of patients with EB esophageal strictures who had been treated with bouginage or colonic transposition. Contract support is envisioned, at an estimated cost of $500,000.

9. Clinical Trial on Efficacy of 13-cis Retinoic Acid in Treating Keratinizing Disorders. The efficacy of 13-cis retinoic acid in the treatment of ichthyosis and other keratinizing disorders would be assessed with a multicentered, randomized, double-blind, placebo-controlled crossover trial. The cooperative agreement mechanism would be used, with support for all the centers totaling $1,000,000.

Mr. Early. Doctor, will any significant research initiative currently underway be halted or seriously delayed due to FY87 funding levels?

Dr. Shulman. Yes, to the extent that research project grants are reduced, in general, initiatives will be effected since they are conducted through that mechanism.

Mr. Early. To what extent will there be major reductions in the scope of ongoing or new initiatives because of the FY87 funding levels?

Dr. Shulman. I believe that the lists of research initiatives we just provided you, sir, is a fair summary of the scientific opportunities that will be affected by FY 1987 funding levels.

Mr. Early. For the record, provide a list of these along with a brief description and the amounts associated with each initiative.

Dr. Shulman. These are the same as provided above, sir.

SPECIALIZED CENTERS OF RESEARCH (SCORs)

Mr. Dwyer. The House report on the FY 1986 Labor-HHS-Education bill called for an assessment of the feasibility of establishing Specialized Centers of Research (SCORs) for research on rheumatoid arthritis, osteoarthritis and osteoporosis. That report was recently submitted to the Committee, and it indicated that use of the SCORs would be highly beneficial, given the impact of these diseases on our society and the unprecedented scientific opportunities in these fields of research. What is the estimated amount of funding that would be required to support the SCOR program as outlined in your report to include a minimum of three research centers for each disease?

Dr. Shulman. In order to support three specialized centers of research in each of the areas of osteoarthritis, rheumatoid arthritis and osteoporosis, we have estimated that $7,700,000 will be needed.

Mr. Dwyer. Can an effective SCOR program be initiated on a smaller scale, for example, one or two centers for each of the three priority areas of research? If an effective program can be established with more limited resources, please provide a breakdown of the amounts that would be required.

Dr. Shulman. In order to provide a critical mass of new knowledge, the minimum number of three Specialized Centers of Research for each major disease is necessary.

Mr. Dwyer. Can an effective SCOR program be initiated within the amounts provided in the FY 87 budget request, without compromising other important currently-funded research activities?

Dr. Shulman. No. The 1987 request does not propose establishing a SCOR program; no dollars or numbers for SCORs are included.

Mr. Dwyer. If Congress approves an increase for your Institute above the original 1986 appropriated amount, do you intend to move forward with the proposals outlined in your report, particularly now that arthritis and musculoskeletal diseases hold the status of a separate institute?

Dr. Shulman. Yes, according to the instructions of the committee.

Mr. Dwyer. One of the primary purposes of SCORs is to expedite the transfer of research results to improved health care. How would you assess the situation now concerning the application of new knowledge to improve diagnosis, treatment and prevention of these diseases?

Dr. Shulman. We believe the SCORs will play a key role in the development of new knowledge that can be applied to improve health care. The transfer of these research results will be expedited by the Institute's Information Office and the Arthritis and Musculoskeletal Diseases Clearinghouse.

EPIDERMOLYSIS BULLOSA

Mr. Dwyer. Your justification reports a number of solicitations for studies of epidermolysis bullosa (EB). What has been the response to this request for research proposals on EB?

Dr. Shulman. The September 1984 Program Announcement on Epidermolysis Bullosa resulted in 15 applications being assigned to NIADDK, of which 9 were funded. The January 1986 Announcement is too recent for us to determine the extent of the response.

Mr. Dwyer. I know that diagnosis and understanding of EB among community-based physicians has been a problem. How is the Institute working to improve this situation? Has there been improvement?

Dr. Shulman. We published a pamphlet entitled "Living with Epidermolysis Bullosa" for distribution to both the scientific and lay communities in the hope that this would reach community based physicians as well as the general public. In addition, research on epidermolysis bullosa has been widely reported in scientific and medical journals, particularly in dermatologic and pediatric journals. D.E.B.R.A., the leading voluntary agency devoted to EB, has professional as well as public education as one of its major missions, and has been an extraordinarily effective organization, in my opinion. This new information should reach those physicians who normally care for the majority of these patients. We supported, in conjunction with the National Institute of Child Health and Human Development, a workshop on Morphogenesis and Malformations of Skin. The report of that workshop will be published in pediatric as well as dermatologic journals. The Institute is preparing to award a contract for an EB Registry, which will include support for several clinical sites for the evaluation and enrollment of EB patients. The publicity attendant to the establishment of this registry and the initiation of the registry clinical sites may well enchance awareness by community physicians of the disease.

ESTABLISHMENT OF THE NEW INSTITUTE

Mr. Hoyer. What do you anticipate will be the greatest payoff from the new Arthritis Institute?

Dr. Shulman. Establishment of a separate National Institute of Arthritis and Musculoskeletal and Skin Diseases will highlight and emphasize these disease areas in ways different from when these diseases had a divisional status. This will focus the Department, the NIH, the Congress, scientists, and the public on the public health aspects of these important diseases, and will result in a vitalization of the research programs for which the Institute is responsible. This new focus will move the scientific and medical community more quickly toward finding causes, prevention, and optimal treatments for these important diseases.

Mr. Hoyer. How will the research program and priorities of the new Institute differ from when it was a component of a larger Institute?

Dr. Shulman. The research programs and activities of the new Institute will largely resemble those when these programs were administered by the AMSD Division of NIDDK, because the vast majority of the research projects will be investigator-initiated, as previously. The law covering the new Institute (PL 99-158) does provide for a number of special emphases, such as epidemiology, sports medicine, and bioengineering.

Mr. Hoyer. How do you intend to establish short and long-term priorities for your new Institute?

Dr. Shulman. The legislation establishing the new Institute specifies that a comprehensive national plan be established to make recommendations concerning research in arthritis and musculoskeletal diseases. The Institute's Advisory Council will play a significant role in this planning process as will the National Arthritis Board. The research programs also obtain guidance from advisory groups of eminent scientists in each of the Institute's scientific fields. All of these sources of input will be combined and analyzed, in concert with the health needs of the nation, to formulate both short and long-term priorities for the Institute. These new development and efforts in research planning will await the appointment of the Institute's permanent Director.

Mr. Hoyer. Last year you mentioned a Secretarial initiative in arthritis. How has that affected your program?

Dr. Shulman. The secretarial initiative provided for the additional funding of 25 research grants in arthritis, specifically in three major areas of great importance to arthritis research: rheumatoid arthritis, osteoarthritis, and osteopsorisis.

Mr. Hoyer. Can you tell us of any advances in curing or treating osteoporosis?

Dr. Shulman. Prevention of osteoporosis is the major hope for reducing the impact of this disease. Unfortunately, treatment approaches are not as positive at this point in time. The only therapy that is known to add new bone is by using high levels of fluoride (much higher than in drinking water). The increased new bone produced by supplemental fluoride is somewhat more brittle than normal bone. A large clinical trial to study the effect on fracture incidence by fluoride treatment is about 2 years from completion. Another drug, calcitonin, is approved by the FDA, and is said to reduce the loss of bone in osteoporotic patients. A new nasal form being evaluated in Europe that may be more practical than the current injectable form. Another recently proposed approach to therapy uses a careful timing of activation and depression of bone metabolism to increase bone mass. This coherence method requires further investigation.

Mr. Hoyer. Please tell us if there have been any advances in lupus erythematosus?

Dr. Shulman. There have been several, Mr. Hoyer. Some patients with lupus do not reveal in their serum antinuclear antibodies (more specifically, anti-DNA antibodies) previously considered to be a hallmark of this disease. Instead, they have another antibody, anti-Ro, that has been related to a new clinical form of lupus, termed "Subacute cutaneous lupus erythematosus". These anti-Ro antibodies have recently been found to also cause neonatal lupus (in infants) manifested by heart lesions, with irregular heart beat, as well as skin lesions. Other antibodies have now been related to other manifestations of lupus; anticardiolipin to miscarriages, anticoagulant to thrombosis, and anti-neuronal antibodies to convulsions and/or psychoses. New forms of treatment for lupus nephritis have been developed by both intramural and extramural scientists both in lupus patients and in experimental mouse models of lupus.

Mr. Hoyer. Why does it occur so much more in women? Also, why more often in Black women than White women?

Dr. Shulman. As you know, lupus occurs nine times more frequently in women than in men. Recent research over the past five years has revealed abnormalities in both female and male hormone (estrogens and androgens) metabolism in women with lupus. In addition, data to support linkage to genetic factors, including the sex-linked x-chromosome, are only suggestive and not conclusive. There may be other factors warranting investigation.

Lupus is also three times more common in Black women than in White women, and the mortality is also higher than in White women. The reasons for this are not clear. Meager data do not indicate a high prevalence in African Blacks. Certain socio-economic conditions may be operative and we are pursuing these possibilities.

ARTHRITIS RESEARCH

Mr. Porter. I have followed with great interest Dr. Thomas Brown's research on an antibiotic treatment for rheumatoid arthritis. Is the Institute involved in any way in this kind of research? Do you have any plans for this area?

Dr. Shulman. The question that Dr. Brown has raised, namely that small organisms called mycoplasmas are involved in the etiology of rheumatoid arthritis, is of great interest, and has been reviewed in the past several years and in reports to Congress. These reviews concluded that over the years, there has been considerable interest and research activity regarding the etiologic significance of mycoplasmas in arthritis and in rheumatoid arthritis (RA) in particular. Reports of successful isolation of mycoplasmas from joints of patients with RA aroused interest, but were not validated subsequently by successful replication of these results by other laboratories. Likewise, antibody studies have lent some credence to the hyothesis that mycoplasmas were involved in the pathogenesis of RA, but again, these results have not been consistently reproducible.

Other organisms, such as viruses and bacteria, are similarly being examined to determine if they have a role in causing arthritis. The Institute is currently working with Dr. Brown and his associates and encouraging their plans to submit a revised application which would study this problem specifically.

Last November the Institute held two workshops which examined the possible infectious etiology of early arthritis and concluded there are a number of potential "candidate" organisms which could be implicated and that effective research in this area was indeed possible. Specific research plans and strategies for for detailed investigative searches for infectious agents were formulated and for applying modern tools of biotechnology. Research on the effects of antibiotics on collagenase production are also being carried out in experimental models of arthritis.

Mr. Porter. How many research grant applications are awarded in proportion to the number of clinical trials conducted for arthritis?

Dr. Shulman. In 1985, we awarded 565 total research project grants, of which 18 were clinical studies. Other clinical studies supported that year were: three in research centers and seven within research contracts, as well as three conducted by the Institute's intramural scientists.

Mr. Porter. About how many clinical trials have been conducted in the past 25 years in the area of infectious arthritis? What plans do you currently have for clinical trials in this area?

Dr. Shulman. As classes of antibiotics have been developed over the years, there have been numerous general clinical trials to establish and compare their effectiveness against specific infectious agents (bacteria, viruses). The results of these general trials are applicable to any arthritic condition involving one or another of these infectious agents; and the antibiotic of choice as determined by clinical trials of the antibiotic in combatting the specific bacteria can be used as a basis for treatment. Therefore, few specific trials on infectious arthritis have been needed and, thus, performed. Infectious arthritis is defined as arthritis that has been shown to be caused by an infectious agent, such as one or several forms of bacteria or viruses, that have been identified in the patient's joint fluid or tissues. The offending organism is brought to the joint by the blood or neighboring structures. It usually causes an acute arthritis. It is treated by the appropriate antibiotic for the particular organism that has been grown from the joint specimen.

For major types of arthritis, for which the cause is not known (such as rheumatoid arthritis, ankylosing spondylitis or lupus), there is need for and there has been research seeking to discern one or more infectious agents that may cause or initate the arthritis. In this regard, at a recent workshop this past November, we have developed detailed plans by a group of experts for a thorough search for bacteria, including mycoplasms, and viruses in patients with early arthritis. Research grant applications in these areas of infection and antibiotics in arthritis are encouraged and most welcome.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

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NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

For carrying out Section 301 and Title IV of the Public Health Service Act with respect to arthritis and musculoskeletal and skin diseases, $106,733,000. (Department of Health and Human Services Appropriation Act, 1986.) 1/

1/ This entire activity has been transferred from the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Language Analysis

Language Provision	Explanation
"For carrying out section 301 and Title IV of the Public Health Service Act with respect to arthritis and musculoskeletal and skin diseases...".	These activities were formerly part of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. However, they are now presented separately as a result of enactment of P.L. 99-158, a major provision of which directed the establishment of the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Amounts Available for Obligation 1/

	1985	1986 Revised Estimate	1987 Estimate
Appropriation..................	---	---	$106,733,000
Comparative transfer from:			
National Institute of Diabetes and Digestive Diseases and Kidney Diseases.....................	+108,808,000	+109,788,000	---
Comparative transfer to:			
National Cancer Institute for changes in the Central Services financing mechanisms and formulas......	-688,000	---	---
Subtotal, adjusted budget authority............	108,120,000	109,788,000	106,733,000
Total, obligations...........	108,120,000	109,788,000	106,733,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1985 -- $521,000; 1986 -- $315,000; 1987 -- $315,000.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Mechanism
(Dollars in thousands)

	1986 Appropriation 1/		1986 Available After Sequestering 1/2/		1986 Revised Estimate 1/2/		1987 Estimate	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Grants								
Research projects:								
Noncompeting	383	$55,947	383	$53,541	383	$53,541	389	$54,702
Administrative supplemental	(13)	375	(13)	359	(13)	359	(13)	400
Competing:								
Renewal	99	17,263	99	16,535	87	15,570	74	12,395
New	96	9,803	96	9,392	82	8,845	70	7,314
Supplemental	4	211	4	203	4	191	4	200
Subtotal, competing	199	27,277	199	26,130	173	24,606	148	19,909
Subtotal, research projects	582	83,599	582	80,030	556	78,506	537	75,011
Research centers:								
Specialized/Comprehensive centers	14	10,231	14	9,792	14	9,792	14	9,317
Other Research:								
Research career programs	52	3,562	48	3,409	48	3,409	48	3,409
Minority biomedical research support	(5)	350	(5)	335	(5)	335	(5)	335
Other research related	9	1,175	8	1,124	8	1,124	8	1,124
Subtotal, other research	61	5,087	56	4,868	56	4,868	56	4,868
Total, Research grants	657	98,917	652	94,690	626	93,166	607	89,196

Training								
Individual awards								
Noncompeting	25	624	25	624	25	624	27	680
Competing								
Renewal	---	---	---	---	---	---	---	---
New	12	296	10	257	10	257	8	201
Subtotal, individual	37	920	35	881	35	881	35	881
Institutional awards								
Noncompeting	211	4,759	211	4,759	211	4,759	192	4,307
Competing								
Renewal	16	361	9	185	9	185	24	543
New	4	90	2	42	2	42	6	136
Subtotal, institutional	231	5,210	222	4,986	222	4,986	222	4,986
Total, training	268	6,130	257	5,867	257	5,867	257	5,867
Research and development contracts	7	2,848	7	2,521	7	2,521	6	2,536
					FTEs		FTEs	
Intramural research		6,467		6,189	35	6,189	35	6,181
Research management and support		2,136		2,045	13	2,045	13	2,953
TOTAL		116,498		111,312	48	109,788	48	106,733

1/ Reflects an enacted administrative reduction of $28,000 and a carryover in unobligated funds of $668,000.

2/ Reflects a consultant services (Section 515 of the Treasury-Postal Service Appropriation Act, 1985) withholding of $205,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

CROSSWALK - 1986 Appropriation 1/
(Dollars in Thousands)

PROGRAM ACTIVITY	MECHANISM Research Grants Research Projects	Research Centers	Other Research	Training Programs Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management & Support	Total
Arthritis, Musculoskeletal and Skin Diseases.......	$83,599	$10,231	$5,087	$920	$5,210	$2,848			$107,895
Intramural Research.......							$6,467		6,467
Research Management and Support....								$2,136	2,136
Total..........	83,599	10,231	5,087	920	5,210	2,848	6,467	2,136	116,498

1/ Reflects an enacted administrative reduction of $28,000 and a carryover in unobligated funds of $668,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

CROSSWALK - 1986 Available After Sequestering 1/ 2/
(Dollars in Thousands)

	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management & Support	Total
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional				
Arthritis, Musculoskeletal and Skin Diseases.......	$80,030	$9,792	$4,868	$881	$4,986	$2,521			$103,078
Intramural Research.......							$6,189		6,189
Research Management and Support....								$2,045	2,045
Total...........	80,030	9,792	4,868	881	4,986	2,521	6,189	2,045	111,312

1/ Reflects an enacted administrative reduction of $28,000 and a carryover in unobligated funds of $668,000.

2/ Reflects a consultant services (Section 515 of the Treasury-Postal Service Appropriation Act, 1985) withholding of $205,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

CROSSWALK - 1986 Revised Estimate 1/ 2/
(Dollars in Thousands)

	MECHANISM								
	Research Grants			Training Programs		Research and Development	Intramural	Research	
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	Contracts	Research	Management & Support	Total
Arthritis, Musculoskeletal and Skin Diseases.......	$78,506	$9,792	$4,868	$881	$4,986	$2,521			$101,554
Intramural Research.......							6,189		6,189
Research Management and Support....								2,045	2,045
Total...........	78,506	9,792	4,868	881	4,986	2,521	6,189	2,045	109,788

1/ Reflects an enacted administrative reduction of $28,000 and a carryover in unobligated funds of $668,000.
2/ Reflects a consultant services (Section 515 of the Treasury-Postal Service Appropriation Act, 1985) withholding of $205,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis and Musculoskeletal and Skin Diseases

CROSSWALK - 1987 Congressional Justification
(Dollars in Thousands)

	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management & Support	Total
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional				
Arthritis, Musculoskeletal and Skin Diseases.......	$75,011	$9,317	$4,868	$881	$4,986	$2,536			$97,599
Intramural Research.......							$6,181		6,181
Research Management and Support....								$2,953	2,953
Total...........	75,011	9,317	4,868	881	4,986	2,536	6,181	2,953	106,733

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Summary of Changes

1986 Current estimated obligations	$109,788,000
1987 Estimated obligations	106,733,000
Net change	-3,055,000

	1986 Base	Change from Base
Increases:		
A. Built-in:		
1. Within-grade increases	$1,000,000	+$33,000
2. Federal Employees Compensation Fund increase	10,000	+2,000
3. FTS rate increase	35,000	+1,000
4. Payment for centrally furnished services	3,296,000	+118,000
5. Increased costs of laboratory supplies, materials and other expenses	3,034,000	+125,000
6. Initial costs of creating new Institute management structure	8,234,000	+1,000,000
Subtotal		+1,279,000
B. Program:		
1. Research projects:		
a. Noncompeting continuations converting from competing status	55,274,000	+24,325,000
b. Competing (new, renewals and supplementals)	23,232,000	+19,909,000
2. Research centers:		
a. Noncompeting continuations converting from competing status	9,092,000	+666,000
b. Competing (new and renewals)	700,000	+4,550,000
3. Other Research:		
a. Noncompeting continuations converting from competing status	4,053,000	+815,000
b. Competing (new and renewals)	815,000	+785,000

Summary of Changes -- continued

	1986 Base	Change from Base
4. Individual training awards:		
a. Noncompeting continuations converting from competing status....................	524,000	+624,000
b. Competing (new and renewals).................	257,000	+201,000
5. Institutional training awards:		
a. Noncompeting continuations converting from competing status....................	4,759,000	+227,000
b. Competing (new and renewals).................	227,000	+679,000
6. Research and development contracts:		
a. Continuations..............	2,171,000	+459,000
Subtotal.............		+53,240,000
Total increases....		+54,519,000
Decreases:		
B. **Program:**		
1. Research projects:		
a. Noncompeting continuations converting to competing status....................	55,274,000	-24,497,000
b. Competing converting to noncompeting status......	23,232,000	-23,232,000
2. Research centers:		
a. Noncompeting continuations converting from competing status....................	9,092,000	-4,991,000
b. Competing (new and renewals).................	700,000	-700,000
3. Other Research:		
a. Noncompeting continuations converting from competing status....................	4,053,000	-785,000
b. Competing (new and renewals).................	815,000	-815,000
4. Individual training awards:		
a. Noncompeting continuations converting from competing status....................	624,000	-568,000
b. Competing (new and renewals).................	257,000	-257,000

Summary of Changes -- continued

	1986 Base	Change from Base
5. Institutional training awards:		
a. Noncompeting continuations converting from competing status	4,759,000	-679,000
b. Competing (new and renewals)	227,000	-227,000
6. Research and development contracts:		
a. Continuation	2,171,000	-94,000
b. New	350,000	-350,000
7. Intramural research: Program decrease in lower priority areas		-121,000
8. Research management and support: Program decrease in lower priority areas		-258,000
Subtotal		-57,574,000
Total decreases		-57,574,000
Total, net change		-3,055,000

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Budget Authority by Activity
(Dollars in thousands)

	1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate		1987 Estimate	
	Amount	Amount	FTEs	Amount	FTEs	Amount
Arthritis and musculoskeletal and skin diseases.........	$107,895	$103,078		$101,554		$97,599
Intramural research..........	6,467	6,189	35	6,189	35	6,181
Research management and support......	2,136	2,045	14	2,045	14	2,953
Total obligations..	116,498	111,312	49	109,788	49	106,733
Unobligated balance, start of year..........	---	---		---		---
Unobligated balance, lapsing.	---	---		---		---
Total..........	116,498	111,312	49	109,788	49	106,733

NOTE: All 1986 columns reflect an enacted administrative reduction of $28,000.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Obligations by Object

	1985 Actual	1986 Estimate	1987 Estimate
Full-time equivalent of permanent positions..............................	48	48	48
Full-time equivalent of all other positions......................	52	52	52
Total compensable work years..........	1	1	1
Average ES salary......................	$66,232	$66,232	$66,232
Average GS grade.......................	9.14	9.14	9.14
Average GS salary......................	28,224	28,224	28,224
Average salary, grades est. by act of July 1, 1944 (42 USC 207)...........	35,361	35,361	35,361
Average salary of ungraded positions..	23,206	23,206	23,206
Personnel compensation:			
Permanent positions.................	1,241,000	1,450,000	1,850,000
Positions other than permanent......	461,000	465,000	470,000
Other personnel compensation........	100,000	105,000	110,000
Special personnel services..........	102,000	102,000	102,000
Subtotal, personnel compensation..	1,904,000	2,122,000	2,532,000
Personnel benefits.....................	280,000	312,000	372,000
Travel and transportation of persons..	76,000	86,000	97,000
Transportation of things..............	21,000	24,000	27,000
Rent, communications and utilities....	259,000	295,000	332,000
Printing and reproduction.............	16,000	18,000	20,000

Obligations by Object - continued

	1985 Actual	1986 Estimate	1987 Estimate
Other services:			
Project contracts....................	$2,013,000	$2,521,000	$2,536,000
Centrally furnished services........	3,022,000	3,223,000	3,336,000
Standard level user charge.........	140,000	73,000	78,000
Other...............................	992,000	1,130,000	1,271,000
Supplies and materials.................	656,000	747,000	840,000
Equipment..............................	179,000	204,000	229,000
Grants, subsidies and contributions...	98,562,000	99,033,000	95,063,000
Total......................	108,120,000	109,788,000	106,733,000

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Significant Items in House Appropriations Committee Reports

Item	Action taken or to be taken
1986 House Report	
Arthritis Centers	
1. "The Committee continues to be concerned about the need to strengthen the arthritis and musculoskeletal diseases research program, and, therefore encourages the Institute to explore the feasibility of establishing specialized centers of research in these high priority areas. The Committee will expect a report on this matter before next year's hearings." (page 48).	1. A report endorsing the scientific feasibility and appropriateness of a specialized centers program focused on rheumatoid arthritis, and osteoarthritis is being prepared for transmission to the Committee.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Significant Items in Senate Appropriations Committee Reports

Item	Action taken or to be taken
1986 Senate Report	
Epidermolysis Bullosa Research	
1. The Committee is encouraged that the NIH allocated $2,600,000 to epidermolysis bullosa-related research in fiscal year 1985, and urges that this encouraging initiative be continued. The Committee directs that not less than $750,000 shall be for direct intensified research on this devastating disease." (page 73).	1. The additional $750,000 has been set aside and research efforts are being expanded in epidermolysis bullosa.
Lupus Research	
2. "... the Committee... urges the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases [NIADDK] to continue to give a high priority to lupus research as well as coordination with other National Institutes of Health [NIH] programs." (page 75).	2. Under P.L. 99-158, the Secretary is establishing a Lupus Erythematosis Coordinating Committee with the director of this institute as chairperson.

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1986 Amt. Authorized	1986 Revised Estimate	1987 Amt. Authorized	1987 Estimate
Research and Investigation........	Section 301	42 § 241	Indefinite	$103,921,000	Indefinite	$100,866,000
National Institute of Arthritis and Musculoskeletal and and Skin Diseases...............	Title IV	42 § 285d	Indefinite		Indefinite	
National Arthritis and Musculoskeletal Disease Programs........................	Title IV	42 § 285d-1	Indefinite		Indefinite	
Research and Training.............	Title IV	42 § 285d-2	Indefinite		Indefinite	
Data System and Information Clearinghouse...................	Title IV	42 § 285d-3	Indefinite		Indefinite	
Interagency Coordinating Committees......................	Title IV	42 § 285d-4	Indefinite		Indefinite	
Arthritis and Musculoskeletal Disease Demonstration Programs..	Title IV	42 § 285d-5	Indefinite		Indefinite	
Multipurpose Arthritis and Musculoskeletal Disease Centers.	Title IV	42 § 285d-6	Indefinite		Indefinite	
Advisory Board....................	Title IV	42 § 285d-7	Indefinite		Indefinite	
National Research Service Awards..	Title IV Part F	42 § 288	$244,000,000 1/	5,867,000	$260,000,000 1/	5,867,000
Total Budget Authority..........				109,788,000		106,733,000

1/ This training authority is shared with other research training programs of the National Institutes of Health, the Alcohol, Drug Abuse and Mental Health Administration and the Health Resources and Services Administration.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1986				115,830,000 1/
1986 Sequester	4,981,000			
1986 Proposed Rescission	1,524,000			
1987	106,733,000			

1/ Reflects a comparative transfer of $115,830,000 from the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases for creation of the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Justification

	1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate		1987 Estimate	
	Amount	Amount	FTEs	Amount	FTEs	Amount
Arthritis and musculoskeletal and skin diseases.......	$107,895,000	$103,078,000		$101,554,000		$ 97,599,000
Intramural research.......	6,467,000	6,189,000	35	6,189,000	35	6,181,000
Research management and support....	2,136,000	2,045,000	14	2,045,000	14	2,953,000
Total.....	116,498,000	111,312,000	49	109,788,000	49	106,733,000

General Statement

The National Institute of Arthritis and Musculoskeletal and Skin Diseases conducts and supports research on many of the most debilitating diseases affecting the public health. The Institute supports basic and clinical research on a number of diseases including arthritis, diseases of the musculoskeletal system, and diseases of the skin, as well as on the normal structure and function of joints, muscles, bones and skin. Basic research involves a wide variety of disciplines, including immunology, genetics, biochemistry, molecular biology, virology, and pharmacology. The importance of these research areas was recognized by the Congress and the President with the enactment of P.L. 99-158, a major provision of which directed the establishment of a separate institute, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Significant new insights into immune mechanisms have strongly implicated them in the cause or aggravation of a number of chronic diseases, including rheumatoid arthritis and lupus erythematosus. Other avenues of immunology as it relates to arthritis research include the role of humoral and cellular immune abnormalities in the pathogenesis of various rheumatic diseases; mechanisms by which mediators of inflammation, such as the prostaglandins and leukotrienes, promote and regulate inflammatory reactions in arthritis; and immunogenetic factors underlying susceptibility to arthritis.

The use of new techniques in molecular genetics has made possible the identification of genetic factors associated with increased risk for developing certain diseases; definition of specific gene defects in inherited disorders; and determination of DNA sequencing of genes that code for substances of potential therapeutic value. Other specific interests of NIAMS in this area include the structure and expression of collagen genes, and tissue typing of populations at increased risk for developing rheumatic diseases, connective tissue diseases, and skin diseases. The Institute also supports investigations of the ultrastructure and pathophysiology of collagens, proteoglycans, and other components of connective tissue; and metabolic derangements underlying gout/pseudogout and osteoarthritis.

Musculoskeletal disease research includes studies of the basic structure of bone and cartilage, metabolic bone diseases, fractures and the healing process, prostheses and relevant biomaterials, biomechanics and bioelectric phenomena, bone transplantation, the physiology of normal and abnormal gait, and inherited connective tissue diseases. In dermatology, investigations are progressing on a wide range of problems including psoriasis, atopic and contact dermatitis, fatal blistering "bullous" diseases, the ichthyoses (scaling diseases), acne, and vitiligo. Scientists are striving to clarify the roles of immunopathology, phototoxicity, and metabolic derangements in causing these disorders, and are having increasing success in doing so by employing the various basic scientific approaches of immunology, biochemistry, and molecular biology.

In carrying out its research mission, the Institute supports both research and research training projects through the use of grants and contracts. The NIAMS also conducts basic and clinical research at its intramural facility in Bethesda, Maryland.

Overall Budget Rationale

The 1987 request for this activity reflects a net decrease of $3,055,000. Of this total, $3,495,000 applies to research project grants. These levels will be achieved by limiting indirect costs and by negotiating direct costs downward. The request will support 148 competing project grants at an average cost of $134,520. This represents a 5.4 percent decrease in average costs from 1986, and an 12.8 percent reduction from full recommended levels. Historically, these reductions have averaged 3 to 4 percent. The request will support 389 noncompeting project grants at an average cost of $140,622. This represents a 0.6% increase in average costs from 1986 and an 13.3 percent reduction from full commitment levels. Historically, these reductions have averaged 1 percent.

The request for research centers is $9,317,000, which will support 14 centers, the same number as in 1986, at $475,000 below the 1986 level. This represents a downward negotiation of 20% from approved or committed levels, as compared to a 13% reduction in 1986.

Research career awards and research training will be maintained at the 1986 levels. Research and development contracts will increase by $15,000 from 1986, to pay the increasing committed costs of clinical research efforts, while one less contract will be supported.

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Intramural research will be conducted at a level of $6,181,000, or $8,000 below 1986. In order to cover the unavoidable costs of mandatory items, it is expected that $121,000 worth of program decreases will be made in lower priority areas.

Research management and support functions in 1986, at a level of $2,045,000, represent the transfer to the newly created Institute of extramural program staff directly related to the Arthritis, Musculoskeletal and Skin Diseases programs. The 1987 request of $2,953,000 constitutes a net increase of $908,000 over 1986 which is a combination of three amounts. In order to implement the second stage of creating the necessary structure for managing an Institute, $1,000,000 has been added. To provide for mandatory increases in existing program costs, decreases of $258,000 will be made in lower priority areas.

Program Accomplishments

Arthritis, Musculoskeletal, and Skin Diseases

New insights are being gained regarding the cause, progression, and treatment of arthritis, musculoskeletal, and skin diseases. Promising basic research cuts across many fields including immunology, genetics, cell biology, and virology. Research into the etiology of the rheumatic diseases has been significantly advanced by refined understanding of the mechanisms of inflammation, better characterization of the immune response system, and the discovery of possible disease-initiating agents.

Rheumatoid Arthritis: A growing body of evidence implicates microorganisms--bacterial, viral, or mycoplasmal--in rheumatoid arthritis (RA). The prevailing theory among those researching the infectious connection is that one or more of these organisms precipitate immune responses that induce arthritic symptoms in genetically predisposed persons. NIAMS grantees have reported evidence of a candidate virus in the etiology of RA. A three-year collaborative study has led to the recognition that a DNA parvovirus, RA-1, is provisionally linked with human rheumatoid arthritis. RA-1 has been identified in samples of joint tissue from patients with rheumatoid arthritis. On the other hand, RA-1 virus has not been identified in synovial tissue of patients with another major kind of arthritis, osteoarthritis. The exact relationship of RA-1 to rheumatoid arthritis is the object of intense scientific efforts.

In other research, employing an experimental model of rheumatoid arthritis, NIAMS-supported investigators have determined that inflammation may not be an early primary causative factor, but rather a late, and thus perhaps secondary, component of joint pathology in this disease. These findings emanate from studies in a very useful animal model, the inbred MRL/l mouse, which spontaneously develops arthritis and serum rheumatoid factors in large amounts. These scientists reported that the first pathologic change in the joints of MRL/l mice is proliferation of synovial lining cells, followed by early destructive changes in adjacent cartilage. Thereafter, inflammation develops and cartilage destruction proceeds. Thus, inflammatory cell infiltration appears late in the process, after joint destruction has begun. The disease process in MRL/l mouse animal model appears to be similar to that seen in patients, making this an excellent model for studying rheumatoid arthritis.

In addition to these exciting advances in understanding the cause and progression of rheumatoid arthritis, hope is offered in improved treatment of patients afflicted with the disease. Several NIAMS-supported clinical studies have determined that low doses of the drug methotrexate are very effective in treating severe rheumatoid arthritis, unresponsive to other second-line medications such as gold compounds or d-penicillamine. Patients treated with methotrexate had significant reduction in disease activity in their joints, with minimal side effects. The drug appears to be a disease-modifying agent, not just palliative. Additional studies are being planned on this drug to determine its long-term efficacy and safety.

Lyme Disease: Solving the puzzle of Lyme Disease took researchers some seven years, but their success in piecing together the clues provides an excellent illustration of the importance of both basic and clinical research in characterizing a disease. This disease was first identified in 1975. Its hallmark is the development of an acute arthritis and in some, a chronic, destructive arthritis that resembles rheumatoid arthritis. NIAMS-supported investigators reported in 1978 that the mode of transmission of the disease is a tick. By 1980 they determined that antibiotics could provide relief from the symptoms. The cause of Lyme Disease was pinned down when other scientists isolated the spirochete bacterium first from the tick and then from patients with Lyme Disease. Shortly thereafter, a blood test measuring antibodies to the spirochete was developed to enable detection of early cases. In the latest developments, scientists have further delineated antibiotic treatments for early-stage Lyme Disease and for a more extensive form of the disease, which also includes neurologic and cardiac involvement.

Systemic Lupus Erythematosus: Systemic lupus erythematosus (SLE) is a chronic, inflammatory, immune-mediated, connective tissue disease involving several organs of the body. It affects young women primarily and is of undetermined origin. Treatment of severe cases can be difficult and can include life-long maintenance with steroids, which often generate disabling and serious side effects. SLE is characterized by excessive production of antibodies, such as anti-DNA antibodies, which are directed against the body's own tissues or chemicals, such as DNA circulating in the blood or residing in the kidneys. Antibodies combine with the antigens to form immune complexes (e.g., DNA-anti-DNA), which damage the kidney and other organs. For this reason, SLE has been considered to be an autoimmune disease, characterized by antibodies reacting against self. Important research has been conducted utilizing the new hybridoma methodology; monoclonal antibodies against DNA and other nuclear antigens have been prepared. Monoclonal anti-DNA antibodies recently have been found to be polyspecific, that is, they react not only with DNA, but with other polynucleotides and even with phospholipids. Immunizing rabbits with one of these phospholipids, cardiolipin, produces not only anti-cardiolipin antibodies, but also anti-DNA antibodies. An exciting implication of this research is that the antibodies involved in the disease process in lupus arise not only from a conventional immune response to DNA, but the trigger for the immune response from a cross-reacting antigen may be from the environment, from outside of self.

Other investigators in this field have reported a research finding that may lead to a more sensitive test for lupus or provide additional evidence of genetic predisposition to lupus. This involves structuring an antibody against a specific part of another antibody, the idiotypic part; this is the specific portion of the antibody that determines its specific immunologic action. Monoclonal anti-idiotype antibodies have been prepared that recognize the idiotype of anti-DNA antibodies in 80 percent of patients with SLE and anti-DNA activity. In a large study of lupus families, many unaffected family members of lupus patients had high reactivity with an anti-idiotype that recognized antibodies against DNA in SLE patients. These studies may have uncovered a fundamental genetic defect in SLE. Moreover, anti-idiotypic DNA antibodies may provide an index of activity in SLE and prove useful in monitoring therapy in this disease.

Previously, two main subgroups of lupus have been recognized: systemic lupus erythematosus, a potentially serious disease involving many organs of the body (including skin) and associated with antinuclear antibodies (including DNA); and discoid lupus erythematosus, which is more benign, affecting only the skin, without antibodies or other immunologic reactions. NIAMS-supported researchers have recently identified and defined a third type of lupus termed "subacute cutaneous lupus erythematosus." Patients with this form of the disease have an extensive, often photosensitive dermatitis, less involvement of organs than in SLE, and negative anti-nuclear antibody tests. Many of these patients do have antibodies against the Ro antigen. This disease, therefore, differs both clinically and immunologically from SLE.

These same researchers have identified the Ro antigen in an additional type of lupus--neonatal lupus (lupus in infants). A mother who has lupus or carries lupus antibodies produces neonatal lupus in her newborn. The two main features associated with neonatal lupus are skin rash and cardiac arrhythmia, an irregularity in the heartbeat. Researchers have now postulated that the lupus skin lesions and the cardiac conduction defect are the result of the transplacental passage of a pathogenic antibody, anti-Ro. Both mothers and affected infants have antibodies against Ro antigen in their blood. These antibodies disappear from the infant usually within six months but persist in the mother. Both of these findings, identifying subgroups with "subacute cutaneous lupus erythematosus" and neonatal lupus, have implications with respect to prognosis and treatment; they also accelerate research on mechanisms by which immunologic factors are related to the causation of SLE.

Osteoarthritis: Osteoarthritis is the most common form of arthritis, and its causes remain obscure. In July 1985, the NIAMS sponsored a workshop on osteoarthritis at which recognized experts in the disciplines of epidemiology, anatomy and pathology, biochemistry, biomechanics, inflammation, and clinical medicine assembled in workgroups to address eight key topics relating to osteoarthritis. Comprehensive reports from these discussions were assembled and reviewed at the workshop. The final report of the workshop is being prepared and will serve both to disseminate the state-of-the-art in osteoarthritis research and to suggest and encourage new directions for research in this important disease. NIAMS-funded researchers, in multidisciplinary studies, are determining relationships between mechanical properties and biochemical constituents of cartilage. Other grantees are making significant contributions to research on osteoarthritis by developing various animal models of this disease, and examining the efficacy of various commonly used treatments. In other efforts, initial research results from a prospective five-year longitudinal study of over 500 running enthusiasts over 50 years of age and matched controls indicate that such running does not appear to be an excessive risk factor for the development of osteoarthritis. If these initial findings are confirmed after completion of the larger prospective study, this represents good news for the increasing number of "mature" Americans staying fit by running.

Osteoporosis: Osteoporosis is a disorder in which bone mass decreases; as a result, the bones become weak and are unusually susceptible to fractures. Osteoporosis is the underlying cause of 70 percent of all bone fractures in elderly persons. It is a common condition that affects both postmenopausal women especially and the elderly in general. The economic impact of osteoporosis to the nation is enormous, at an estimated cost of nearly $4 billion each year. In people of all ages, bone is continuously breaking down and being replaced by new bone. In osteoporosis, the loss of bone exceeds the formation of new bone. NIAMS-supported scientists have reported research results on major issues in understanding osteoporosis, including the relative role of aging as compared to the role of estrogen deficiency in postmenopausal bone loss. Their study suggests that estrogen deficiency, rather than age, is the predominant cause of bone loss during the first decade after menopause. These results offer some insights into preventing this major national health problem. Other research involves the optimal calcium intake, mode and degree of physical exercise, and role of sodium fluoride in preventing and treating osteoporosis.

Osteogenesis Imperfecta: Osteogenesis imperfecta (O.I.) is a common heritable disorder of connective tissue. Significant advances are being reported in defining specific genetic, molecular, and biochemical defects in certain forms of this disorder. Collagen defects are generally accepted as major factors in the pathogenesis of O.I. For the first time, the etiologic bases of some forms of O.I. have been described in molecular terms. Characterizing the specific molecular defects in the genetic coding for the synthesis of collagen may be the beginning of identifying the specific mutations in some forms of O.I.; may lead to the identification of additional defects in other forms; and facilitate the development of methods to repair or replace defective collagen genes.

Skin as an Immunologic Organ: Allergic contact dermatitis is the most common immunologic disease affecting the skin. Practical methods for determining the existence of allergic phenomena to a specific chemical have been in use for over 50 years. Recently, the cellular and immunologic bases for these allergic phenomena have become better understood. NIAMS-supported investigators have reported that three different cell types in the outer layer of skin are involved in cutaneous immunologic reactions. The cells that are critical in the mediation of allergic contact dermatitis have been identified. Identification of the distinct cells involved in the induction, elicitation, and eventual suppression of delayed contact hypersensitivity in skin may provide new means of addressing not only the pathogenesis but also the management of contact dermatitis. In addition, recent research on the Langerhans cell, found to be important in presentation of antigen, is providing new understanding of immunologic mechanisms generally. The application of this new knowledge may provide the means of impeding the induction of contact dermatitis from allergies, some of which are common important environment allergens in industry.

Epidermolysis Bullosa: Epidermolysis bullosa (EB) comprises a group of heritable diseases in which skin and other epithelial surfaces, including the mucous membrane of gastrointestinal and respiratory tracts, form blisters and become denuded after physical trauma of varying degrees. While the disorder is uncommon, the morbidity and mortality rates are high. Recently, Institute-supported scientists have shown that new techniques of immunohistochemistry are useful in the diagnosis of EB; the time required to establish an accurate diagnosis has been significantly shortened. Fluorescent-labeled antibodies have been developed which can identify the normal components of the basement membrane zone of the skin, and in that way, allow direct visualization of the specific anatomic level of blistering in EB. In other research important to EB, studies are defining an underlying abnormality in collagenase, a specific enzyme in the dermal layer of skin. The heterogeneity of this disorder clinically is reflected at the molecular level; not only are there mutations in which an abnormal enzyme is formed, but some patients have an abnormality in the regulation of enzyme production. An interesting outcome of this basic research is the observation that the drug phenytoin (or Dilantin) has an ameliorative effect in vitro by blocking collagenase. Moreover, phenytoin has been found to be clinically useful in reducing blistering in many patients. These research advances, therefore, have improved understanding both of specific defects in EB, and also of the normal structure and function of the epidermal basement membrane zone. This, in turn, has led to improved diagnosis and treatment of EB and other diseases of the basement membrane zone.

Intramural Research

The Division of Intramural Research pursues basic and clinical research projects relating to the areas of arthritis, musculoskeletal, and skin diseases. Intramural research activities include investigations of animal models of systemic lupus erythematosus and arthritis; involvement of the immune system in various rheumatic diseases; muscle biology; clinical research on arthritis ard other rheumatic diseases; and fundamental studies in molecular biology, immunology, biochemistry, pathology, and biophysics.

Rheumatoid Arthritis: Intramural scientists have developed an animal model for rheumatoid arthritis that provides a powerful tool for studying the development of this disease. They found that the administration of cell wall fragments from certain bacteria will induce first an acute and then a chronic arthritis by causing the synovium (the joint membrane or lining) to proliferate and become inflamed. The proliferating inflamed synovium then erodes the surrounding bone and cartilage, leading to joint destruction. This process resembles human rheumatoid arthritis in its clinical, pathological, and immunological characteristics. No evidence of bacterial cell-wall fragments has, as yet, been found in humans. By studying this animal model, scientists hope to learn more about the triggering events that cause synovial proliferation and inflammation, identify different phases of the disease, and characterize the genetic, immunologic, and pathophysiologic factors that determine the specific mechanisms that produce the arthritis.

Systemic Lupus Erythematosus: Patients with systemic lupus erythematosus (SLE) suffer from inflammation of the joints, kidneys, skin, heart, lungs, central nervous system, and other organs. Clinical features include arthritis, kidney failure, anemia, fatigue, rashes, seizures, and psychoses. Lupus is especially common in teenage and young adult females, although it can affect people of all ages. The multiplicity of abnormalities in these patients has made investigation into the disorder difficult and makes it one of the most challenging disorders for clinicians and for basic scientists. The causes of the disease are still not known, but recent advances have begun to allow a more directed approach to the problem. These advances have occurred in the scientific areas of humoral and cellular immunology and immunogenetics. Insights derived from extensive research on inbred mice with lupus have helped greatly to provide a framework for many of the approaches to patients with SLE.

NIAMS intramural scientists have clearly shown that genetic factors play an important role in this disorder: certain genes may produce a generalized immune abnormality, whereas others may lead to production of specific autoantibodies. Environmental triggers and bacterial and viral illnesses have been shown to be capable of increasing the expression of illness. The effect of the X chromosome-linked gene, xid, upon the immune system in mice has been under intensive study for the past 10 years. It has been found that xid causes impaired maturation of certain subpopulations of B cells (antibody-producing lymphocytes, found in blood and lymphoid organs). An exciting advance in this field by intramural scientists is that SLE in these inbred mice can be largely overcome by the introduction of the single protective gene, xid. The results of this and other research suggest that only a subpopulation of B cells may be responsible for antibody production.

Polymyositis: Polymyositis is an uncommon, chronic disease characterized by inflammation of muscles. Researchers have demonstrated that the autoantibodies in SLE and related diseases including polymyositis are produced in response to a specific stimulus and probably do not arise from a general "turning on" of the immune system. NIAMS intramural scientists have produced a monoclonal antibody to a specific enzyme, histidyl-tRNA synthetase, in mice. The laboratory is seeking to determine if the presence of antibodies against this enzyme may be the result of interaction between the enzyme and a virus. Clues suggesting that this may be the case include: (1) in polymyositis, virus particles have been found inside inflamed muscle cells; (2) in children with myositis, serum antibodies induces possible exposure to coxsackie virus-B, suggesting an antecedent coxsackie viral infection leading to myositis; and (3) evidence suggests that a virus resembling coxsackie can interact with a specific enzyme. One research hypothesis is that a virus may enter a cell and interact with the enzyme to cause the immune system to produce antibodies against the enzyme, subsequently leading to polymyositis.

Muscle Biology: Intramural scientists are steadily increasing knowledge of the structure and function of muscle fibers, discovering intricate physical and chemical relationships involved in mobilizing energy for muscles to contract and generate body motion. Part of this research focuses on the crossbridges that form the attachments between the muscle filaments. Through the study of individual muscle fibers, NIAMS scientists have discovered that crossbridges are characterized by different states of attachment/detachment between filaments. The rate of attachment/detachment can change according to the presence of certain nucleotides. Continued work, utilizing X-ray diffraction technology, thermodynamic relationships, and mechanical measurements, will further extend fundamental knowledge of muscle action, leading to increased understanding of diseases that affect muscles.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Arthritis and Musculoskeletal and Skin

1987 Authorization: Indefinite.

Budget Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987 Estimate	Increase or decrease
$107,895,000	$103,078,000	$101,554,000	$97,599,000	-$3,955,000

Purpose and Method of Operation

Basic, developmental, and applied research is fostered in three major program areas in this Institute through the use of investigator-initiated research grants, research career development awards, center grant awards, intramural research programs, and research and development contracts. National Research Service Awards support the training of individuals for full-time academic careers in research and teaching.

Arthritis and Related Diseases

Arthritis and other rheumatic diseases afflict over 36 million Americans. Among the more than 100 kinds of arthritis and related disorders are such diseases as rheumatoid arthritis, osteoarthritis, juvenile arthritis, systemic lupus erythematosus, gout, spondylitis, and many inherited and acquired connective tissue disorders, such as scleroderma. Arthritis is the nation's primary crippler, causing increasing numbers of persons to leave work before normal retirement age. The resultant loss of earnings has been estimated at $25 billion a year. Arthritis is reported to affect more than 40 percent of people over age 65. In addition, an estimated 250,000 children have arthritis or a related joint disease. Some 100,000 of these children will carry serious handicaps into adulthood. In addition to disability, some forms of juvenile arthritis can cause kidney disease, blindness, and even premature death. NIAMS research is organized to be responsive to these public health needs and comprises a broad spectrum of fundamental research on causes of the diseases, complemented by clinical research on the treatment and possible prevention of specific rheumatic diseases.

Rheumatoid Arthritis: Rheumatoid arthritis (RA) is an inflammatory disease of joints characterized by pain, stiffness, deformities, and disability. RA remains the major crippling disorder among the rheumatic diseases. Findings from research over the past few years make it likely that rheumatoid arthritis is caused not solely by a single microorganism (virus, bacterium) or a deranged factor in the immune system, but rather, by different agents generating immune responses that later lead to chronic inflammation in those with genetically-determined abnormal immune regulation and biochemical abnormalities. NIAMS grantees have recently reported research findings that may give new insights into the mechanism of joint destruction in RA. Using the MRL/l mouse model of rheumatoid arthritis, this laboratory has documented that the pathologic changes in the joints of these mice can be divided into three sequential stages: (1) proliferation of synovial lining cells, (2) continued synovial cell proliferation and early destructive change in adjacent cartilage, and (3) development of inflammation, diminution of synovial cell proliferation, and further cartilage destruction. Inflammatory cell infiltration appeared late in the process and after destruction of joint cartilage had begun. Thus, this study indicates that early joint destruction is more closely related to the presence of proliferating synovial cells than to the presence of inflammation. These findings steer research on RA in a new direction--a search for agents or mechanisms causing the early synovial cell proliferation.

In FY 1986, the NIAMS sponsored a two-component workshop, assembling basic scientists and clinicians who are recognized experts in the field of infectious agents and their role in early arthritis. This workshop reviewed the latest basic and clinical research developments and made specific, detailed recommendations for future investigations on potential infectious agents as causes of rheumatoid and other forms of arthritis. The Institute intends to pursue the very valuable recommendations made and to exploit the many new basic research methodologies that have been developed recently and are now available. These include the new technologies of monoclonal antibodies, recombinant DNA, and molecular biology, as well as utilizing experimental animal models such as the MRL/l mouse, which has been shown to be an excellent model for studying rheumatoid arthritis.

NIAMS grantees have reported that total lymphoid irradiation therapy, an extremely effective treatment for Hodgkin's disease and other lymphoid tumors, when used for severe refractory rheumatoid arthritis, can produce long-term relief from arthritis; however, demonstrated side effects may limit the usefulness of this treatment. Researchers are attempting to modify the treatment regimen to reduce adverse side effects. In other clinical studies, both oral and injectable gold compounds have been reported to be effective in the treatment of active rheumatoid arthritis in a multicenter, clinical, double-blind drug trial. In addition to providing evidence of the effectiveness of gold therapy, this study also documented the sensitivity and usefulness of employing health status indicators in detecting meaningful improvements in outcome in a formal clinical trial of therapy for a chronic disease. Traditional estimates of health improvements have dealt with "objective" measures of disease activity, such as physical examination and laboratory tests. The Institute encourages the use of health status measures as a reliable adjunct to physical determinants of disease activity in studying the efficacy of new treatments.

Systemic Lupus Erythematosus: Systemic lupus erythematosus (SLE) is a chronic, inflammatory, immune-mediated, connective tissue disease involving several organs of the body. It is primarily a disease of young women and its cause is unknown. SLE is considered to be an autoimmune disease, characterized by antibodies reacting against self. One of its serious features is involvement of the brain resulting in seizures and/or organic psychoses. Recently, NIAMS researchers have shown that lupus patients with neuropsychiatric manifestations have antibodies circulating in their blood that destroy lymphocytic blood cells. These anti-lymphocyte antibodies have been shown to cross-react with brain cells in these patients. Researchers now believe that the antibodies against lymphocytes in the blood also attack brain cells, and may be responsible for psychoses in some lupus patients. The Institute intends to pursue further research on the possible pathogenetic role of the antibodies, including investigation of antibody reactivity directed against neurotransmitter receptors that regulate brain function. Studies will seek to characterize the antigens shared by neurons in the brain and by lymphocytes resulting in antibodies that cross-react with both cells. The potential link between altered immune regulation and nervous system dysfunction in SLE will continue to be explored.

Monoclonal antibodies against the specific reactive parts of other antibodies in SLE are of keen interest to researchers. The antigen Ro has been found to trigger the production of antibodies in subacute cutaneous lupus erythematosus and in neonatal lupus. Further studies will be encouraged by the Institute to exploit fully monoclonal antibodies as research tools for elucidating further the pathogenesis of the disease. Such studies have important implications for understanding pathogenetic mechanisms in autoimmunity, resulting in new insights into the causes of SLE and other autoimmune diseases.

In one of the most exciting avenues of lupus-related research, immunologically specific therapy for systemic lupus erythematosus is being developed. Since several investigators have established that antibodies to DNA are important, the question now being studied is whether, in experimental animal models, the disease can be attacked by manipulating the immune system. Previously, researchers were working to block emergence of the disease in animal models by giving anti-DNA antibodies early in life. The studies undertaken most recently involve determining whether production of antibodies can be eliminated in mice by altering the antigen and making the animal tolerant to the altered antigen. In the future, such forms of immunotherapy will continue to be tested in experimental animals and with cultured human lymphocytes. Investigations of tolerance in human lymphocytes to nucleic acid antigens may provide the required data base for the induction of unresponsiveness to DNA in patients with SLE.

In addition, the NIAMS sponsored a conference in FY 1986 on Educational Strategies for Improving the Outcome of Lupus in High Risk Populations. This conference convened an interdisciplinary group of experts who: (1) described factors that affect the outcome of SLE in various high risk populations; (2) considered educational strategies that could be undertaken at present that might improve disease outcome; and (3) suggested ideas for additional information needed from research and additional educational programs that could be conducted in the future.

Ankylosing Spondylitis: A striking association between the genetic marker HLA-B27 and ankylosing spondylitis (inflammation of the spinal vertebrae) and related spondylarthropathies (such as Reiter's syndrome) was established more than a decade ago. This striking association is a clue to the pathogenesis of these spondylitic diseases, but further studies are needed. Fertile areas for intensified research in this field include defining the role of the immune system; locating the triggering agent for the disease, infectious or environmental; and determining whether the major genetic factor is HLA-B27 itself or a closely linked gene. Recently, Institute-supported scientists reported a new marker in the blood in ankylosing spondylitis patients using a test that identifies antibodies to antigens associated with chromosomes. They demonstrated that a high number of antibodies in the sera of patients with ankylosing spondylitis reacts with antigens present on the chromosomes of Drosophila. This novel antibody reaction in patients with ankylosing spondylitis could be detected before clinical parameters for a definite diagnosis became apparent. This test, therefore, may provide a new method for achieving early diagnosis of this disease.

Multidisciplinary Studies: Cooperative multidisciplinary efforts central to understanding rheumatic diseases will continue to focus on genetic predisposition and immunogenetic relationships. The NIAMS plans to pursue recommendations from the FY 1986 workshop on Immunogenetics in Rheumatic Diseases, which will bring together scientists in the areas of immunogenetics, immunopathology, and immunological expression of rheumatic diseases, to relate what is known in basic immunogenetics to the pathophysiology of specific rheumatic diseases. The Institute will also exploit the latest advances in biotechnology, especially monoclonal hybridoma technology and high resolution molecular separation techniques whose potential applications in selected major rheumatic diseases will be explored in the FY 1986 conference.

The Multipurpose Arthritis Centers (MACs) also provide important opportunities for multidisciplinary research achievements. Each center has three components—biomedical research, professional and patient education, and health services research projects. Center funds are used to support pilot and feasibility studies in arthritis-related areas that utilize innovative multidisciplinary scientific approaches to arthritis research problems. Research in MACs encompasses a wide range of disciplines and interests from basic biomedical research to health services research. The Institute looks to the MACs in the future for continued research excellence, important research advances, and a uniquely coordinated approach to basic and applied arthritis research.

The Cooperative Systematic Studies in the Rheumatic Diseases remains a program of vital importance to the Institute. Studies on the evaluation of potentially effective new drugs and drug toxicity in arthritis patients are essential. Investigations within this program include definitive studies of promising new drugs, controversial treatments, and accepted, but unproven, treatments. Long-term studies by a consortium of cooperating clinics, coordinated by a center with strong biostatistical expertise and data management, are important components of this program. Well-designed systematic cooperative studies have yielded important information about the efficacy of antirheumatic drugs (cyclophosphamide, d-penicillamine, oral gold, and methotrexate) and the requirements for such studies are expected to continue.

Musculoskeletal Diseases

Orthopaedics research supported by the NIAMS encompasses both fundamental and clinical studies of bone and cartilage and other supporting structures in normal and disease states. The scope of this research includes basic biology of bone and cartilage; metabolic bone diseases; fractures and the healing process; prostheses and relevant biomaterials; biomechanics and bioelectric phenomena; bone transplantation; the physiology of normal and abnormal gait; and inherited connective tissue diseases.

Osteoarthritis: Osteoarthritis (OA), degenerative joint disease, is the most common form of arthritis, affecting some 16 million Americans, most of whom are over 50 years old. Several biochemical and biomechanical changes have been identified in this disease. An objective of high priority for the NIAMS is to stimulate research on the etiology of osteoarthritis, in addition to investigations on the underlying initiating events, cause of disease progression, and difficulty of cartilage repair. Studies are also needed on the role of aging of cartilage, and determinants of the inflammatory component in osteoarthritis. In July 1985, the Institute supported a major workshop on the etiopathogenesis of osteoarthritis, which served to address key questions and to identify new research approaches on osteoarthritis. Recommendations from leading experts in the field assembled for this conference are serving as a basis for the technical portion of a Request for Applications (RFA) to be issued by the Institute this year. This request had three objectives: to encourage studies on pathogenetic mechanisms in osteoarthritis, to promote epidemiological research studies, and to promote interdisciplinary investigations. The Institute will continue to pursue promising avenues of research in this field, as recommended by the Workshop in the areas of biochemistry, bioengineering, epidemiology, bone-cartilage interactions, extracartilaginous tissues (synovium, tendons, ligaments), repair of cartilage, results of trauma, the role of aging, and the conditions of inflammation in osteoarthritis.

Osteoporosis: Osteoporosis is the leading underlying cause of bone fractures. It affects as many as 15 to 20 million Americans, primarily postmenopausal women, causing spinal crush fractures, and hip and wrist fractures. About 1.3 million fractures attributable to osteoporosis occur annually. The condition affects over fifty percent of women above age 45 years and 90 percent of women above age 75. Many factors have been related to the development of osteoporosis, which is characterized by the production of less dense, and thus, weaker bone. Studies have shown that deficiency of estrogen in postmenopausal women, or women whose ovaries have been removed surgically, is clearly related to an accelerated loss of bone mass. Estrogen supplementation in postmenopausal women has been determined in clinical studies to be effective in the prevention of osteoporosis; the side effects, including an increased risk for endometrial cancer, however, have reduced the general acceptance of this treatment. It is possible that even lower doses of estrogen may prove to be more acceptable, or the addition of progestins may eliminate some of the side effects and risks from estrogen. The Institute intends to encourage research on the risks and benefits of various combinations and doses of these female hormones, and ascertain optimal delivery schedules and routes. Also to be pursued are investigations on abnormalities of basic bone metabolism in osteoporosis; evaluating the architectural strength of bone as it matures; understanding the rapid bone loss occurring at the menopause; and determining the influence of microfractures and their healing in osteoporosis.

Osteogenesis Imperfecta: Osteogenesis imperfecta (O.I.) is a genetic disease that causes fragile bones with premature fractures and defects in other connective tissues. It is reported to be the most common heritable disorder of connective tissue. An estimated 30,000 people in the United States have osteogenesis imperfecta. A major defect seems to be in genetic coding for one or more of the helical chains that comprise collagen. A major advance in this area has been the recent documentation of four of these specific genetic defects. In FY 1985, the NIAMS issued a Program Announcement whose objectives were to encourage additional research on genetic defects in osteogenesis imperfecta, define other specific defects in milder forms of O.I., and promote initial efforts toward genetic counseling and the development of therapeutic measures, such as replacement for defective collagen genes.

Bone Metabolism: The continuous remodeling of bone is a complex, multifactorial process. An important advance in understanding this process came with the recent identification and isolation of several proteins that control bone remodeling. Research has been aided by the development of several bone cell lines and the technology to culture bone in a cell-free medium.

Osteoclasts are cells responsible for resorption of bone. These cells are part of a complex resorption and formation cycle that is closely regulated in normal bone. In disorders such as osteopetrosis and Paget's disease, osteoclasts function abnormally and result in mechanically weak and misshapen bones. Recent advances in developing pure cultures of osteoclasts and monoclonal antibodies for osteoclast cell surface receptors have improved the productivity of research efforts. Paget's disease remains, however, a major medical problem affecting millions of persons, mostly elderly. Recognizing that there is a deficiency in understanding of both the disease itself and its treatment, the NIAMS convened a workshop in FY 1985 on Osteoclast Function and Paget's Disease. The Workshop successfully served to define recent advances and provided guidance for recommendations for new research approaches in the future.

Low Back Pain: Impairments of the spine comprise the most common cause of limitation of activity among persons 17 to 45 years of age. Low back pain affects 8 of 10 adults in the United States, and its total economic impact exceeds $10 billion annually. Both the etiology of low back pain and its treatment are uncertain. The complexity of anatomic supporting structures and neurologic pathways have made research on low back pain difficult. A workshop is being planned to assess recent progress in low back pain research, as a follow-up to a previous workshop on this topic. New research directions will be formulated by the participants, with emphasis on the importance and planning of multidisciplinary research approaches.

Athletic Injuries: With increased national interest in exercise and physical fitness, researchers supported by the NIAMS are directing new efforts towards the responses of muscle to various forms of exercise and physical training. Muscles enlarge as a result of weight-lifting and a long-held concept is that the mechanism for this is splitting of muscle fiber with a subsequent increase in the number of fibers. Recent findings, however, have shown that the number of muscle fibers is established early in skeletal maturity and remains relatively constant thereafter. The mechanism for increasing muscle size, therefore, appears to be enlargement of individual muscle fibers. Knowledge gained from such basic studies of muscle physiology may contribute greatly to the design of more efficient training programs for athletes and those interested in promoting musculoskeletal physical fitness. These studies may also contribute to the development of optimal rehabilitation programs. The NIAMS intends to encourage additional fundamental studies in exercise physiology and pathophysiology, including research on muscles, tendons, and ligaments. The Institute will promote much needed further research on sports injuries.

Skin Diseases

Diseases of the skin exact a high toll in terms of disfigurement, discomfort, disability, and even death. Investigations are under way on a wide range of dermatological problems including psoriasis, vitiligo, acne, atopic dermatitis, lupus erythematosus, scleroderma, and potentially fatal "bullous" diseases such as pemphigus and epidermolysis bullosa. Employing sophisticated new laboratory techniques, scientists are working to clarify the roles of immune-mediated responses, phototoxicity, and metabolic derangements as causes of these disorders. Special emphasis will be given to applying monoclonal antibodies, gene cloning, and related techniques to basic research on macromolecular components of the skin in health and disease. This research will enable delineation of control mechanisms whereby hormones, enzymes, and specific minerals affect normal skin and cutaneous diseases, and will lead to eventual improvement in the care of patients with skin diseases.

Skin as an Immunologic Organ: Researchers are increasingly interested in studying the skin as an immunologic organ, particularly in allergic contact dermatitis. Current research concerns the role of Langerhans cells in antigen presentation within skin, and chemical intermediates produced during antigen processing in skin. The cascade of chemical events involved in inflammation is also a continuing promising avenue of research. Inflammatory processes, mechanisms of sensitization, and expression of delayed hypersensitivity are important in many cutaneous diseases. Occupational skin diseases, which are predominantly irritant in nature, and in the form of allergic contact dermatoses, comprise the largest single cause of industrial and occupational diseases. Consequently, they have a very large economic impact nationally. The Institute intends to encourage researchers to investigate mechanisms of primary irritant dermatitis, with emphasis on industrial and environmental exposures; to explore further etiopathogenetic mechanisms of allergic contact hypersensitivity and methods of intervention to prevent either initial sensitization or subsequent development of dermatitis; and to elucidate processes of inflammation in both irritant dermatitis and allergic dermatitis.

Epidermolysis Bullosa: Epidermolysis bullosa (EB) is a group of hereditary diseases in which skin and other epithelial surfaces, including the mucous membrane of the gastrointestinal and respiratory tracts, form blisters and become denuded after physical trauma of varying degrees. In many cases, symptoms of the diseases resemble severe burns. As many as 20 genetically distinct forms of EB have been described, some of which often prove fatal early in childhood or are severely disabling. Recent advances in monoclonal antibody technology, tissue culture, blotting techniques, and sophisticated electron microscopy have provided an impetus to accelerated research in epidermolysis bullosa. Moreover, studies of EB are now providing highly important information elucidating the normal structure and function of the skin's basement membrane zone.

The basic underlying cause of epidermolysis bullosa may involve either a structural defect in proteins or other components that bind epidermis to the underlying dermis, or an abnormal enzyme that degrades one or more of those structural elements. As a result, the attachment between the epidermis and dermis is weakened. The Institute issued Program Announcements in both FY 1984 and FY 1985 encouraging researchers to study epidermolysis bullosa and the biology of the basement membrane zone. The initial pathologic changes of EB appear to occur in the basement membrane zone. The Institute, therefore, seeks studies aimed at achieving a better understanding of pathophysiologic mechanisms and/or structural abnormalities which contribute to the onset of EB. In addition to its clear importance to EB, research investigations of the basement membrane zone are relevant to other important areas in biomedical research, including burns, wound healing, development of artificial skin, and the structural/functional relationships of collagen and collagenolysis and their genetic control. The NIAMS encourages proposals that utilize research advances in genetics, pathology, cell and developmental biology, biochemistry, and immunology as they relate to various types of EB and the biology of the basement membrane zone.

The NIAMS is currently developing a registry of well-characterized patients with different forms of epidermolysis bullosa. Patients will be requested to contribute specimens and/or be followed as part of diagnostic protocols, participate in research on pathogenesis, and participate in therapeutic protocols. This registry will serve to increase information on the genetics of EB with respect to family patterns and sporadic occurrence of the disease; determine incidence and prevalence statistics of EB by clinical and genetic types in statistically sufficient numbers; and obtain longitudinal data on carefully selected subsets of patients with EB to determine the natural history of disease and the value of various therapeutic interventions in well-defined specific forms of epidermolysis bullosa.

Retinoids: Retinoids are a highly promising group of agents that have proven effective in treatment of severe cystic acne resistant to other therapies. Studies now suggest that these agents may also be beneficial in treating psoriasis, some keratinizing disorders, and systemic lupus erythematosus. In addition, recent studies have demonstrated the beneficial effects of retinoids in tissue culture, organ culture, and animal model systems. One research group has reported that retinoids appear to suppress cholesterol synthesis in cultured human keratinocytes, while a second group of Institute grantees found that retinoids have anti-inflammatory effects on human mononuclear and polymorphonuclear leukocytes. The Institute is encouraging researchers to discover mechanisms by which retinoids confer therapeutic benefits in severe acne and keratinizing disorders; to identify in detail both short-term and long-term side effects; and to maximize therapeutic efficacy.

Wound Healing: The problem of wound healing, specifically as it relates to decubitus ulcers and leg ulcers, is an area of great medical concern and financial burden. The NIAMS is encouraging collaboration between researchers in diverse specialties to collaborate with bone scientists working on cell migration and macromolecular structures involved in wound healing. Avenues to be pursued include epithelial cell migration, macromolecular structures involved in wound healing as delineated by new investigative techniques; investigations of blood flow; and clinical interventions designed to foster wound healing.

Rationale for the Budget Request

The FY 1987 request for this activity reflects a decrease of $3,955,000. Research project grants will experience a greater negotiated reduction in 1987 than in 1986 and 19 fewer will be supported. The same number of research centers, research career awards and research trainees will be funded, although the size of research center awards will be reduced by a greater percentage than in 1986. In order to provide for increasing committed costs in research and development contracts, particularly clinical research, one fewer award will be made in 1987, although the contracts funding total will rise by $15,000.

AMS

Impact Data	1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987 Estimate
Res. proj. grants				
Number	582	582	556	537
Amount	$83,599,000	$80,030,000	$78,506,000	$75,011,000
Res. centers				
Number	14	14	14	14
Amount	10,231,000	9,792,000	9,792,000	9,317,000
Other research				
Number	61	56	56	56
Amount	5,087,000	4,868,000	4,868,000	4,868,000
Training programs				
Number	268	257	257	257
Amount	6,130,000	5,867,000	5,867,000	5,867,000
Research and dev. contracts				
Number	7	7	7	6
Amount	2,848,000	2,521,000	2,521,000	2,536,000
Total	107,895,000	103,078,000	101,554,000	97,599,000

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

Intramural Research

1987 Authorization: Indefinite.

Budget Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987 Estimate	Increase or decrease
$6,467,000	$6,189,000	$6,189,000	$6,181,000	-$8,000,000
		(FTEs: 35)	(35)	(—)

Purpose and Method of Operation

Intramural activities provide many examples of outstanding research in the basic and clinical sciences, leading to important advances in medicine. Research efforts are directed at understanding rheumatoid arthritis, systemic lupus erythematosus, and other types of arthritis; connective tissue disorders; cellular and chemical immunity; the underlying processes that produce autoimmunity and the role of autoimmunity in disease; the development of inflammation and its role in disease; and the structure and function of muscles. Ongoing intramural projects include the study of an animal model of rheumatoid arthritis that provides valuable insights into the development and progression of rheumatoid arthritis; fundamental research on the causes of systemic lupus erythematosus (SLE); clinical testing of therapeutic agents for rheumatoid arthritis and SLE; and research into the cause and progression of polymyositis. Progress in all these areas is based on a multidisciplinary approach involving experts in immunology, biochemistry, molecular biology, genetics, and biophysics. Close cooperation among NIAMS scientists and investigators from other institutes, agencies, and academic institutions further enhances and fosters NIAMS research efforts.

IgE Receptors: Antibodies and antibody-like molecules are the only molecules known to mediate the exquisite specificity of the body's immune defense system. The molecules act as receptors on cell surfaces or in solution, where they activate so-called "biologic effector systems." An understanding of the precise mechanisms by which these molecules act may allow scientists to develop therapeutic manipulations of the immune system. NIAMS intramural scientists are investigating one such effector system in depth, the IgE-mast cell system, with the aim of achieving a better understanding of the molecular mechanisms involved. Activation of the mast cell leads to release of a variety of substances which contribute to inflammation. These cells are increasingly being implicated in some of the connective tissue disease (lupus, arthritis) and inflammatory bowel disease. IgE is also the immunoglobulin antibody most directly involved in allergic reactions and serves as the protective antibody in parasitic infections. The principal focus of this NIAMS project is how mast cells and basophils are activated by IgE. Recent important advances include the determination that IgE acts via its own cell receptor; the recently acquired ability to purify the receptor protein;

characterization of the protein's structure in considerable detail; and development of the mechanism to insert the protein into artificial membranes. These advances may have broader implications, since IgE-mediated stimulation of mast cells/basophils may have a counterpart in antibody-mediated reactions on a wide range of other cells.

Rheumatoid Arthritis: The genetic, immunologic, and pathophysiologic characterization of the host parameters that determine arthritis susceptibility are continuing. Because there is immune system involvement in rheumatoid arthritis, intramural scientists are also studying whether agents such as cyclosporin A, that have regulating effects on the immune system, may prove beneficial in treating this crippling disease. NIAMS scientists are testing the efficacy and toxicity of cyclosporin A in active rheumatoid arthritis patients who have not benefited from other forms of treatment. Preliminary results in several patients show a favorable therapeutic response to cyclosporin A.

Systemic Lupus Erythematosus (SLE): NIAMS intramural researchers have established the important role of genetic factors in SLE. These investigators are building on the important research advances that SLE in human mice can be largely overcome by the introduction of a protective gene, xid; that xid cause~~s impai~~red maturation of some subpopulations of B cells (antibody-producing lymphocytes); and the suggestion, therefore, that only a subpopulation of B cells may be responsible for antibody production. It is anticipated, therefore, that it will be possible to identify in humans with SLE a subpopulation of B cells responsible for the production of autoantibodies characteristic of this disease. If a specific marker for such cells could be found, intervention strategies could be developed for this selective elimination. Therapy with an appropriate monoclonal antibody becomes, therefore, a possibility. Such an approach might prove useful for other immune-mediated diseases as well. Other recent advances in molecular genetics will be applied first to mice with lupus, and if promising, in the future to human SLE. Future investigations will also seek a better understanding of how the disease gets started and how flares of disease activity are triggered. Such an understanding might enable the development of preventive measures for SLE.

Polymyositis: This uncommon, chronic disease is the focus of intense research efforts in NIAMS intramural laboratories. Researchers have produced a monoclonal antibody to a specific enzyme, histidyl-tRNA synthetase, in mice and studies now are aimed at determining if antibodies against this enzyme may result from the enzyme interacting with a virus. Using a particular virus, these NIAMS intramural scientists have successfully induced myositis in mice. Researchers intend to continue to explore the interaction between the virus and the enzyme, histidyl-tRNA synthetase. The effect of other virus variants on other enzymes will also be pursued. NIAMS scientists will also investigate the natural course of viral infection by studying the life cycle of the viruses in inflamed muscles. Collaborative efforts will be pursured with other NIH laboratories to extend these studies in an intense search for viral involvement in polymyositis.

Mechanism of Muscular Contraction: NIAMS intramural scientists are deeply involved in investigating the mechanism of muscle contraction. Muscle fibers consist of different protein-containing filaments formed in a lattice pattern. The different proteins form crossbridges between filaments, thereby allowing the muscle to contract. NIAMS scientists have developed an X-ray detector that records and analyses the structure of the crossbridges. By examining crossbridge structures under different physiologic conditions, scientists have learned more about how muscle fibers produce force and motion, and how mechanical responses are regulated. This research provides valuable insight into the basic function and structure of muscle, enabling scientists to apply this knowledge to understand muscular diseases and suggest possible therapeutic approaches. NIAMS will continue to encourage work in this important area of muscle biology.

Rationale for the Budget Request

Intramural research will be conducted at a level of $6,181,000, or $8,000 below 1986. In order to cover the unavoidable costs of mandatory items, it is expected that $121,000 worth of program decreases will be made in lower priority areas.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Research Management and Support

1987 Authorization: Indefinite.

Budget Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987 Estimate	Increase or decrease
$2,136,000	$2,045,000	$2,045,000	$2,953,000	+$908,000
		(FTEs: 14)	(14)	(—)

Purpose and Method of Operation

This activity provides support for the immediate office of the Institute Director and for certain administrative and business management functions including financial management, personnel management, property control and travel audit and control, which are most efficiently performed as centralized functions. This staff continues to assume new responsibilities and reporting functions such as those required under the Freedom of Information Act and the manpower productivity measurement program.

A major portion of the resources of this activity is devoted to review and approval of grants functions including professional and suporting personnel who are responsible for the administration of the Institute's several grants activities. They assist in the planning and development of programs in research, training, and fellowships that will best serve to accomplish the desired results in the areas of disease interest for which this Institute is responsible; review and evaluation of research and training grant applications for presentation to the National Advisory Arthritis Council; required Council staff assistance; liaison with applicants, grantees, other components of NIH and the Department, advisory bodies, and interest organizations; and continuous surveillance of scientific information relevant to all transactions.

The other major functions under this activity are the review, management and negotiation of research and development contracts of the categorical program areas, and support of the national advisory board in arthritis.

Rationale for the Budget Request

Research management and support functions in 1986, at a level of $2,045,000, represent the transfer to the newly created Institute of extramural program staff directly related to the Arthritis, Musculoskeletal and Skin Diseases programs. The 1987 request of $2,953,000 constitutes a net increase of $908,000 over 1986, which is a combination of three amounts. To implement the second stage of creating the necessary structure for managing an Institute, $1,000,000 has been added. To provide for mandatory increases in existing program costs, decreases of $258,000 will be made in lower priority areas.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Detail of Permanent Positions

	1985 Actual	1986 Estimate	1987 Estimate
ES-4	2	2	2
GS/GM-15	4	4	4
GS/GM-14	4	4	4
GS/GM-13	4	4	4
GS-12	0	0	0
GS-11	4	4	4
GS-10	0	0	0
GS-09	3	3	3
GS-08	3	3	3
GS-07	9	9	9
GS-06	6	6	6
GS-05	3	3	3
GS-04	0	0	0
GS-03	0	0	0
GS-02	0	0	0
Subtotal	42	42	42
Grades established by act of July 1, 1944 (42 U.S.C. 207):			
Surgeon General Grade	0	0	0
Assistant Surgeon General Grade	0	0	0
Director Grade	3	3	3
Senior Grade	2	2	2
Full Grade	0	0	0
Senior Assistant Grade	0	0	0
Subtotal	5	5	5
Ungraded	1	1	1
Total permanent	48	48	48

THURSDAY, MARCH 13, 1986.

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

WITNESSES

DR. PIERRE F. RENAULT, ACTING DIRECTOR, NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

DR. JAMES B. WYNGAARDEN, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

L. EARL LAURENCE, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

DONALD F. CYPHERS, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Mr. EARLY [presiding]. The meeting will come to order. We are pleased to have Dr. Pierre Renault, the Director of the National Institute of Diabetes and Digestive Kidney Diseases with us. Would you give us your statement, please?

Dr. RENAULT. Thank you, Mr. Chairman. I am privileged to be here to report on the accomplishments and plans of the National Institute of Diabetes and Digestive Kidney Diseases, and the scientists that we support. I have with me Mr. Cyphers, our Budget Officer, and Mr. Laurence, our Executive Officer. The NIADDK supports a diverse, but comprehensive program of research on some of our Nation's most severe and debilitating chronic diseases. We support and conduct research in diabetes, endocrin and metabolic diseases, digestive diseases and nutritional disorders, and kidney and urologic and blood diseases. In the diabetes area, in the last year we have initiated a full-scale clinical trial testing the hypothesis that keeping a diabetic patient's blood sugar as close to normal as possible will prevent the development of the complication of diabetes. This trial—the Diabetes Control and Complications Trial—will involve 1,400 patients in 26 treatment centers around the Nation. With this trial, we expect to answer one of the most fundamental issues in the treatment of diabetes and we also expect it to have a major positive impact on the treatment of diabetes in the United States. In metabolic diseases, you have heard about the discovery of the genetic marker for the cystic fibrosis gene. This is a quantum leap toward finding the cause and hopefully the cure for this disease. In digestive diseases, we have begun work on a liver transplantation data system. Liver transplantation is a procedure that cannot be studied as a randomized clinical trial. The Liver Transplantation Data System will allow transplant surgery teams to systematically collect information on the patients that they treat and thereby learn from their experience and the experience of others. Most of the liver transplantation units around the nation have voluntarily participated in the planning of this system indicating the importance they feel this information will have in improving our ability to do successful liver transplantations. In kidney disease, there is another example of modern molecular genetics. The gene which causes polycystic kidney disease has been located. This disease is a major cause of end-stage renal disease; and, hopefully, finding this gene will lead to the cause and the cure of polycystic kidney disease. However, this discovery is of immediate importance to the families afflicted with this disorder. Polycystic kidney disease does not become manifest until early adulthood, and prior to this discovery individuals and families lived with the unknown. Now individuals who are afflicted as well as those who are not can be identified. For those who have the gene, interventions can be tried to prevent the development of the disease. Those who can be shown to be free of the gene need no longer fear that they may develop the disease, freeing them to live a more normal life. Finally, the Institute now has underway in collaboration with the Health Care Financing Administration the pilot phase of a major multicenter clinical trial of an nutritional intervention in chronic renal disease. There is mounting evidence that dietary protein has a deleterious effect on kidneys that have been damaged by disease. Waste products of the metabolism of protein increased the blood pressure and flow in the blood-filtering units of the kidney beyond their natural capacity causing their deterioration and, thus, the progressive loss of renal function. The restriction of dietary protein early in the course of chronic renal disease may actually prevent the progression to end-stage renal disease and the need for renal dialysis or transplantation. Mr. Chairman, that completes my statement. I am happy to answer any questions.

Mr. EARLY. Well, we have a lot of questions, Doctor.

[Statement follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Acting Director National Institute of Diabetes and Digestive and Kidney Diseases

As the Acting Director of this Institute, I appreciate the opportunity of discussing with you some of the plans and accomplishments of our extramural grantees and intramural scientists. Our Institute has served as a leader for over 30 years of a broad research effort on some of our nation's most serious and debilitating diseases: diabetes, endocrine, and metabolic diseases; digestive diseases and nutritional disorders; and kidney, urologic, and blood diseases. While progress in knowledge and treatment of these diseases has been steady, in-depth understanding of the causes and progression of these diseases has attended the mobilization of the powerful techniques of modern biomedical research. As a result of NIDDK's intensive investment in basic research, we now have models of the probable sequence of events leading to many of these diseases. I am pleased to be able to present examples of how advances in basic research have progressed in tandem with development of new methods of diagnosis, treatment, and prevention of disease.

Diabetes, Endocrinology and Metabolic Diseases: Progress at the frontiers of medicine is amply evident in research on diabetes, estimated to affect 11 million Americans at a cost of $14 billion annually. Evidence is continually expanding on the aberrant immune response which causes destruction of pancreatic islet cells and therefore loss of insulin-producing capacity in insulin-dependent diabetics. Testing these findings, researchers have demonstrated that a transfusion of peripheral or splenic lymphocytes is able to prevent the development of the disease in diabetes-prone animals. The protective effect of this transfusion lasted for over a year in some cases.

Application of immunologic findings will also determine the success of transplantation of pancreatic islet cells, which holds the promise of restoring near-normal insulin production to individuals with insulin-dependent diabetes. The Institute is supporting efforts to adapt for use in diabetes patients a technique of islet cell grafting which studies in animals suggest may be effective, even in the absence of prolonged immunosuppression.

While the daily existence of an insulin-dependent diabetic may prove restrictive and difficult, it is the complications of diabetes which are devastating and often prematurely fatal. The Institute's Diabetes Control and Complications Trial, designed to determine whether strict control of blood glucose levels can prevent or ameliorate vascular and other long-term complications of diabetes, entered the large scale phase in fiscal year 1986. This phase of the trial will monitor 1,400 patients for five to seven years, and is expected to produce results which may have a major impact on the clinical management of diabetes for many years to come.

The Institute also conducts in its intramural facility in Phoenix, Arizona, a valuable program of epidemiologic and clinical research on the Pima Indian population, a unique, almost genetically pure population which has the highest rate of noninsulin-dependent diabetes in the world. More than twenty years of study has resulted in a wealth of important insights into this disease, including the discovery of a genetic marker which correlates with increased risk of developing diabetes. Researchers hope to use this marker to locate the gene or gene sequence that contributes to the increased predisposition to diabetes in the Pima Indians. In addition, the Institute plans to initiate shortly in this population a multifaceted study of renal disease, diabetic nephropathy, the major cause of death in diabetic Pimas.

The Institute has maintained a long history of leadership in basic and clinical research on endocrine and metabolic disorders. Recombinant DNA techniques have already made possible the synthesis of potentially unlimited amounts of clinically effective insulin, somatostatin, and growth hormone. Institute grantees have recently synthesized growth hormone releasing factor or GRF, a neuropeptide which stimulates the pituitary to produce and release growth hormone. Clinical tests of synthetic GRF showed that it can achieve, in patients with a primary deficiency of this factor, an increase in growth comparable to that seen with growth hormone therapy, but with an approach which promises to be safer, less costly, and more easily administered. An array of potential new therapies are expected to emerge as researchers characterize the physiologic roles in health and disease of other important hormones and determine their genetic blueprints.

Although inherited metabolic disorders are individually uncommon--many are considered "orphan diseases"--approximately 30 to 40 percent of all admissions to children's hospitals and approximately one-third of all infant deaths in the U.S. are attributable to such disorders. Advances in molecular biology and genetics have brought us to the threshold of combating specific inherited metabolic diseases, such as Lesch-Nyhan syndrome, through gene replacement. Each year, such intensive research efforts bring us closer to uncovering the basic metabolic defects in cystic fibrosis (CF), the most common lethal genetic disease in Caucasians. Recently, the Institute has assembled a talented group of intramural investigators and significantly expanded its support of CF research. These intramural scientists have successfully applied a technique, now under further testing, which promises to provide a superior indicator of disease and clinical status in patients with CF. This year has also witnessed the discovery of three markers for the CF gene. While not responsible for CF, these genetic markers have revealed that the CF gene is located on chromosome 7, and their discovery has vastly narrowed the search for the gene responsible for CF.

Digestive Diseases and Nutrition: Digestive diseases rank second only to cardiovascular diseases as the leading cause of disability due to illness in the U.S. These diseases include more than 40 acute and chronic gastrointestinal conditions, burdening our country with costs estimated as high as $50 billion per year. The Institute is encouraging the application of innovative techniques of molecular biology, immunology, and biomedical engineering to understanding, treating, and eventually preventing these illnesses.

A wealth of new findings has been applied to reducing the toll of these diseases. Gallstones, present in 10 percent of the population, can now, in some cases, be treated on an outpatient basis. In the most recent such non-surgical procedure devised, an Institute grantee successfully dissolved gallstones in patients using a solvent called methyl tertiary butyl ether, or MTBE, administered trans-abdominally through a catheter under local anesthesia. Such an alternative to abdominal surgery holds the promise of enormous cost savings and increased safety, especially in individuals at high risk, and far more rapid return to normal activity than is possible now.

New medications and surgical techniques have reduced the number of peptic ulcer patients requiring hospitalization for treatment of their condition by more than 40 percent between 1970 and 1980. NIDDK intramural investigators have obtained positive results in preliminary testing of two additional drugs to treat this disease. Unprecedented progress in preventing and treating ulcers and other digestive diseases may also result from the recent discovery of hormones, usually neuroregulatory peptides, in both the brain and in the digestive tract or its nervous system. These hormones may prove to be the sought-for links between stress factors, the nervous system, and digestive tract function. Using modern molecular biologic techniques, investigators will identify, characterize, and eventually synthesize these substances, investigate their activities, and apply them to therapeutic intervention.

NIDDK's intramural and extramural nutrition research programs underpin research throughout our Institute and NIH. Through basic metabolic and clinical studies, this program is tackling the myriad questions regarding human diet in the maintenance of health and the prevention and management of a wide range of diseases. The Institute's intramural program has contributed greatly to the recent exponential increase in understanding of vitamin D disorders. High priority areas of research will continue to include calcium and vitamin D metabolism, the metabolic and health consequences of polyunsaturated fatty acids, and the development of new techniques of nutritional assessment. NIDDK's continuing assessment of the diet of patients receiving total parenteral nutrition will both improve the effectiveness of this therapy and refine our understanding of human nutritional needs.

Another objective of this program is the control of obesity, a major problem in our society. The recently-reported study of adoptees, which proved definitively that genetic factors, not family environment, determine human fatness or thinness, was partly supported by NIDDK. By narrowing the scope of the population vulnerable to obesity, the results of this study will accelerate more sensible construction and targeting of programs of obesity prevention, and may be instrumental in eventual control of this disorder.

Kidney, Urologic and Hematologic Diseases: Kidney and urologic diseases affect more than 13 million Americans and account for over

80,000 deaths each year. Using the most advanced research techniques, scientists have pinpointed the location of the genetic defect in polycystic kidney disease, characterized by the insidious development of kidney cysts and progressive destruction of kidney function. Because of this information, there is now a diagnostic test to detect individuals affected before kidney destruction occurs. Knowing the genetic defect also clears the way for elucidating the nature of the biochemical defect involved and makes possible eventual prevention of one of the major causes of chronic renal disease. Equally important to the families afflicted with this disorder is the fact that the availability of this test allows physicians to advise family members who do not carry the affected gene.

For the more than 7,000 patients who undergo kidney transplantation each year, substantial progress has recently been made in reducing the associated morbidity and mortality. Further success in kidney transplantation is expected through manipulation at the molecular level of the interaction between the immune system and the transplanted kidney, especially though the use of monoclonal antibodies. These molecules, targeted against the immune cells responsible for transplant rejection, have been shown in clinical trials to achieve a reversal rate as high as 90 percent in ongoing kidney rejection. Additional monoclonal antibodies are now being evaluated in an effort to reduce the adverse side effects of this procedure. A high Institute priority will be to improve the outcome of kidney transplantation in children.

The Institute now has under way, in collaboration with the Health Care Financing Administration, a major multicenter clinical trial to assess the effects of diet therapy on the progression of chronic renal disease. The results of this study are likely to have an important impact on the use of dietary modification in treatment of chronic renal disease.

Urinary tract infections account for much of the renal failure in end-stage renal disease in both adults and children. We are therefore gratified to discover that immunization against the most common offending organism in this condition can be effective. The Institute is also intensifying efforts to follow up on research advances relating to benign prostatic hyperplasia and sexual dysfunction, both important and growing health problems.

Institute-supported scientists have opened a new avenue of therapy for patients with aplastic anemia, a progressive and usually fatal disease typically resulting from an unexplained failure of the bone marrow to produce blood cells. Upon finding that bone marrow failure is not complete or irreversible, but possibly due to an immune response, these investigators tried a new procedure which suppresses the immune system. This procedure restored normal bone marrow function in some of these patients.

This program also has earned the credit for two remarkable advances in molecular genetics. In one, scientists have for the first time altered a specific gene in human cells. This gene, which directs the synthesis of hemoglobin, is the one that is defective in blacks with sickle cell anemia. The second advance involves the cloning of the human gene for erythropoietin, which regulates the production of red blood cells by the bone marrow, and the production of this hormone from these clones. The availability of erythropoietin in commercial quantities will make possible an improved quality of life in patients who are anemic because unable to produce this hormone, including the 70,000 patients in the U.S. who have chronic renal failure.

Conclusion: The accomplishments I have presented were made possible because of a strong commitment to a comprehensive research effort. This effort requires the talent and skill of new investigators. The Institute is making every effort to maintain the momentum of our support of research training and research career awards. We also recognize the important contribution made to the NIDDK program by our centers of research excellence. In the coming year, we will be supporting 31 centers encompassing research in cystic fibrosis, diabetes and endocrinology, obesity, clinical nutrition, and digestive diseases. We are striving to maintain a balance between the fundamental research which is the promise of the future and the clinical research which makes research findings accessible to us now.

Mr. Chairman, the 1987 budget request for this Institute is $418,971,000. I will be pleased to answer any questions.

BIOGRAPHY OF DR. PIERRE F. RENAULT

September 21, 1936. San Francisco, California. Married, three children.

Education: B.S., University of California, San Francisco, 1959. M.D., University of California Medical School, San Francisco, 1962.

Professional History: 1962-63, Intern, University of California, San Francisco. 1963-64, Junior Assistant Resident, University of California, San Francisco. 1964-66, U.S. Navy, Lt., Chief of Medicine, Station Hospital N.A.S., Lemoore, California. 1966-69, Resident, University of Chicago. 1969-70, Director, Northside Clinic, State of Illinois Drug Abuse Program. 1969-71, Instructor, University of Chicago. 1969-71, Assistant Director, Psychiatric Consultation Service, University of Chicago Hospitals. 1971-74, Assistant Professor, Department of Psychiatry, University of Chicago. 1970-73, Consultant to State of Illinois Drug Abuse Rehabilitation Program. 1971-73, Acting Director, Psychiatric Consultation Service, University of Chicago Hospitals. 1973-74, Director of Research, State of Illinois Drug Abuse Rehabilitation Program. 1974-76, Clinical Assistant Professor of Psychiatry, Georgetown University, Washington, D.C. 1974-80, Chief, Clinical Behavioral Branch, Division of Research, National Institute on Drug Abuse. 1974-82, Private Practice of Psychiatry, Chevy Chase, Maryland. 1975-1986, Assistant Professor of Psychiatry, The Johns Hopkins University School of Medicine, Baltimore, Maryland. 1980-82, Associate Director for Medical and Scientific Evaluation, National Center for Health Care Technology. 1982-83, Associate Director for Program Planning and Analysis, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health. 1983-present, Deputy Director, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health. 1984-present, Liaison Psychiatrist, Liver Diseases Section, Digestive Diseases Branch, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health. 1984-present, Medical Staff of the Clinical Center, National Institutes of Health.

Professional Organizations: Washington Psychiatric Society, American Psychiatric Association, Distinguished Affiliate of the Division of Psychopharmacology of the American Psychological Association, American Association for the Advancement of Science.

Honors, Awards: PHS Commendation Medal, 1982.

HEALTH RESEARCH EXTENSION ACT OF 1985

Mr. EARLY. Dr. Renault, I was really pleased with it. NIH gets so repetitious year in and year out. A lot of the time they just talk about research, but I am sure people are concerned about its immediate effect. You said it specifically. I really think that is important. In science, you don't want to mislead anybody; but I think maybe we have been too conservative in not showing a little more light at the end of the tunnel.

Now, the name of your Institute is changed as a result of the Health Research Extension Act, which created a separate Institute for Arthritis and Musculoskeletal and Skin Disease. Does this law contain any other provisions which affect the operations of the Diabetes and Digestive and Kidney Diseases programs?

Dr. RENAULT. Yes, it does. There are several provisions. I think the most notable ones that are going to make a major difference in the way we operate are provisions for data systems in kidney disease, the provision for a kidney urologic disease and hemologic disease coordinating committee, the provision for a clearinghouse for kidney and urologic diseases, and the provision for a National Kidney Advisory Board.

Mr. EARLY. Why don't you, for the record, expand on that with regards to the coordinating committee and the clearinghouse.

Dr. RENAULT. Yes.

[Information follows:]

KIDNEY, UROLOGIC, AND HEMATOLOGIC DISEASES COORDINATING COMMITTEE

The purpose of this Committee is:

1. Better coordination of the research activities of all the national research institutes relating to kidney, urologic, and hematologic disease; and
2. Coordinating those aspects of all Federal health programs and activities relating to these diseases to assure the adequacy and technical soundness of related programs and activities, to provide for full communication and exchange of information necessary to maintain adequate coordination of these programs and activities.

The Committee will be composed of the Director, NIDDK; the Director, Division of Kidney, Urologic, and Hematologic Diseases, NIDDK; the Directors of each of the other national research institutes and divisions involved in kidney, urologic, and hematologic diseases research; the Chief Medical Director of the Veterans Administration; the Assistant Secretary of Defense for Health Affairs (or the designees of such officers) and representation from all other Federal departments and agencies whose programs involve health functions or responsibilities relevant to these diseases, as determined by the Secretary. The Committee will be chaired by the Director of NIH or his designee. The Committee will meet at the call of the Chairman, but not less often than four times a year.

The Committee will prepare an annual report for the Secretary, the Director of NIH, and the National Kidney and Urologic Diseases Advisory Board detailing the work of the Committee. This report will be submitted not later than 120 days after the end of the fiscal year.

NATIONAL KIDNEY AND UROLOGIC DISEASES INFORMATION CLEARINGHOUSE

This Clearinghouse will be established to facilitate and enhance knowledge and understanding of kidney and urologic diseases on the part of health professionals, patients, and the public through the effective dissemination of information.

PERCENTILE RANKS

Mr. EARLY. Now, beginning with the applications that went to the September 1984 Advisory Council, the National Institute of Diabetes and Digestive and Kidney Diseases began to use percentile ranks rather than priority scores as principal measures of scientific merit for all regular research grant applications. Please explain how this system works, if you are using it. I am assuming that you are still using it?

Dr. **Renault**. We are still using it. We originally brought that up to our Council for advice and the Council concurred that we were to try it for two years, to study the effect of that kind of a payment system. We still use priority score as the fundamental measure of scientific merit, and that is a score that is awarded to each application in an initial period of years. But the percentile rank is used to fund applications where we take whatever percentile it is across the board for each study section, each initial review group, and we pay those applications until our money runs out.

Mr. **Early**. What is the advantage of that, Dr. Renault?

Dr. **Renault**. Well, we felt that it would be potentially a more fair system in that all study sections do not award the same priorities or have the same distribution of priorities. Hopefully, if you paid totally by priorities with that money, you would be paying more grants in some areas of science than in others.

Mr. **Early**. Well, should there not be more in certain areas than in other areas?

Dr. **Renault**. Well, there are with the percentile rank as well, but that is also dependent on the number of applications coming to that section. I might add that we don't completely ignore the priority score. Clearly if the percentile rank had us funding at a very high priority score in one area, we would certainly reconsider that.

Mr. **Early**. Do you think it gives the Director more or less independence with regards to grants?

Dr. **Renault** I think it is comparable. I think the discretion of the Director and the staff and the Advisory Council is really in the programmatic area, and these scores and rankings are attempts to measure the scientific quality of the application. What we would tend to do programatically is to look at how much research we are funding in a given area and to look for areas that are under funded and make judgments along that line.

Mr. **Early**. I assume from your comments that you are going to continue the percentile ranking.

Dr. **Renault**. We intend to continue it and we have evaluated it regularly for our Council, and I believe at the September Council meeting we will try to come to a decision on whether or not we will continue to do this.

Dr. **Wyngaarden**. Mr. Early, if I may add to that, in the last couple of years with increasing competition we have found that study sections are grading higher and higher. There has been a certain amount of grade increase. In past years, one could array the scores and they would describe a single curve with a peak in the middle, around 200 or 225. Now we find three curves, with peaks at 150, 300, and 450. The degree of shift has varied from one study section to another; some grade higher than others, rather like school teachers. Without some type of normalization, the study sections that have given higher grades are going to average at a different internal scale and would tend to have more applications funded than those of a study section that grades lower. With normalization, the distribution is about the same in the various programs.

Mr. **Early**. That certainly sounds like a much more favorable approach. To me it appears, Dr. Wyngaarden, it would give you a little more independence.

Dr. **Wyngaarden**. Yes, it does.

Mr. **Early**. What other Institutes are presently using a percentile ranking system?

Dr. **Wyngaarden**. The percentile system is also used by the Heart Institute and Child Health Institute.

Mr. **Early**. Do you know if any of the other Institutes plan to adopt this?

Dr. **Wyngaarden**. We are watching these three Institutes. It is in the way of an controlled experiment. We will determine what the satisfaction is in these Institutes before we make a recommendation for NIH as a whole.

Mr. **Early**. I think that is the right way to go. At this time, I will yield to Mr. Conte.

Mr. **Conte**. Doctor, let me first of all say how sad I was to hear of Dr. Lipsett's passing last November. He was a good man. We always appreciated his advice and counsel when he came to testify for the Child Health Institute and then, later on, for the NIADDK. He is missed here, and I am sure he is missed there at NIH.

Dr. **Renault**. Very much, sir.

Mr. **Conte**. Second, we touched on this this morning and I want to thank you Dr. Renault and Mr. Laurence, and Dr. Shulman, who was here this morning, for meeting with Dr. Ellison last fall on very short notice. I personally appreciated your responsiveness on that occasion.

Dr. **Renault**. Thank you. It was very interesting, actually. It is a fascinating idea.

CYSTIC FIBROSIS

Mr. **Conte**. Thank you. I was very heartened to hear of the development of a genetic marker for cystic fibrosis last fall, and the development of a test for it. Although work in this area has been going on, it appeared to me that the discovery really came as somewhat of a surprise in an area of research that had always been slow to yield breakthroughs in the past. How did that discovery come about?

Dr. **Renault**. Well, I think your observation is correct, that this has been a difficult area. I think that the major reasons that we had this discovery really are the long-standing or long-building commitment to basic research in areas that have produced the technology that allowed us to find this sort of a marker. I think a great deal needs to be done to really find the gene, but we are well on our way.

Mr. **Conte**. Did the Institute support any of the research leading to this discovery?

Dr. **Renault**. I believe we did. I don't have any specifics on that.

Mr. **Conte**. Where would you say that research will go from here on cystic fibrosis?

Dr. RENAULT. Well, finding the gene and, thereby, characterizing the defect will be a major direction that the scientific community will pursue. I think there are other areas of research, as well. We are developing a great deal more information about the actual defects individuals such as afflicted the permeability of cell membranes to ions and getting at the very basis of the disease in chemical terms. I think also from a treatment point of view clearly there is still a great deal of work to be done, although we have achieved quite a bit. Once cystic fibrosis was a disease that was fatal at a very young age, and now individuals are living well on into adulthood. Of course, this area is in antibiotics and treatment of infection. Also early diagnosis, fetal diagnosis, can allow the preparation of a treatment strategy for the child so that treatment can begin very, very early in the child's life. I think that, in itself, should certainly decrease morbidity.

Mr. CONTE. It appears that, after having been reorganized, the Intramural Cystic Fibrosis Program is now fully operational. Tell us a little bit about this program and where is the program heading.

Dr. RENAULT. Yes, sir. I think that this has been one of those initiatives which involve seizing on opportunity and it has been particular gratifying. Because of having a very strong intramural program, especially strong in molecular biology, we were able to ask some of our scientists to pursue the area of cystic fibrosis, to apply some of their ideas and techniques to this area. Clearly, the areas I have already mentioned will be pursued. I think probably one of the most interesting events recently reported to us was of a test for cystic fibrosis, which is based on a test that was really developed to detect colon cancer because there is a mucin protein in the blood that is quite characteristic of that cancer, but it also appears in cystic fibrosis patients and in carriers of the cystic fibrosis gene. This is new research. It is certainly going to take time to be applied in any general way. However, it looks very hopeful to us that with this test we might be able to detect carriers of the gene; and, in doing that, I think again be able to give very important information to the families of these patients.

Mr. CONTE. In the meantime, there have been great advances in patient care. I saw an article in one of the Massachusetts General Hospital publications talking about their program of care for cystic fibrosis patients who range in the ages of 20 to the mid-40s, compared with 30 years ago, when a child born with cystic fibrosis had only a 50-50 chance of reaching one year of age. Is it the effects of cystic fibrosis itself, such as the thickening of the secretions in the lung, or the infections that tend to follow, that tend to cause the most damage and pose the most real challenge in assisting cystic fibrosis patients?

Dr. RENAULT. Yes. Clearly I think this is the case in both damage to the lung and the increased incidence of infection and certain kinds of infection, which are particularly damaging and to the lung; and also the problems in nutrition in cystic fibrosis, where the pancreas—which is, of course, an organ that produces digestive enzymes and is very important in the nutritional process—is damaged very often to a level that it is not functional. Clearly we have worked very hard to improve the nutrition in these patients. We are having a meeting later this year on that very subject: nutrition in cystic fibrosis.

BENIGN PROSTATIC HYPERTROPHY

Mr. CONTE. Last year, Dr. Lipsett talked a little bit about benign prostatic hypertrophy. He mentioned that research was underway on alternatives to surgery, such as a new hormonal way to moderate the condition. Are there any new developments here, and are there viable nonsurgical treatments for this condition?

Dr. RENAULT. We have not developed a new treatment in the last year, but we have accomplished a couple of very important things. I think primarily we have developed some insights into what to study: the important things that should be studied. This should focus the research in this area. Possibly one of the more important things that we have done, though, is we have actually been able to interest researchers who have established reputations studying hormones and hormone receptors, to study male hormones, in the prostate. Male hormones are probably very important in the hypertrophy or the growth of the gland and very little is known about them in the prostate.

Mr. CONTE. Where is the leading work in this area being done?

Dr. RENAULT. There are a number of centers. The two that come to mind are at the University of California-San Francisco where there has been a very major technical advance which is being able to grow the two types of tissues that make up the prostate gland independently and to study them independently, and to study their interaction which, from the scientific point of view, is very important. Another site of continuing interest in BPH has been at Johns Hopkins University.

DIABETES BUDGET

Mr. CONTE. Doctor, what is the size of the Institute's Diabetes program? Has it grown over time?

Dr. RENAULT. The size of our Institute's Diabetes program we estimate, in this year, is $103 million. Last year the actual figure was $103,977,000. It certainly has grown over time. I have a trend analysis here, which begins in 1983. At that time, the total diabetes budget in our Institute for the Diabetes program was $84 million. So you could say it has grown in that period of time, over the last three years, from $84 to $103 million.

Mr. CONTE. And you expect to spend about that in 1987?

Dr. RENAULT. In 1987, our estimate is $101 million.

JUVENILE DIABETES

Mr. CONTE. So we are going back a little. Has any more progress been made in arresting the destruction of the insulin-producing cells in the juvenile onset of diabetes through the use of immune therapy?

Dr. RENAULT. Well, as you know, this is an area of continuing interest. There are two types of diabetes: adult onset and juvenile diabetes or insulin-dependent diabetes. In the latter condition, there is an attack on the insulin-producing cells in the pancreas. In many patients this attack appears to be autoimmune. It appears that the body creates antibodies against its own tissue and destroys these cells. One of the insights that we have gotten into this whole process is being able to identify, through typing of tissue in individuals, some individuals in whom this appears to be a primary phenomenon and in others the antibody is possibly not the most important factor, and the distruction of insulin producing cells is perhaps more related to a viral infection or some other destructive, exogenous agent. There are some ongoing studies trying to suppress this auto immune reaction. Notably there is one study in Florida using Cyclosporin early in the course of insulin-dependent diabetes. These treatments are they are still very experimental, but it would appear that the disease process can be arrested and certainly ameliorated. In other words, you can cut down on the antibody production and the destruction of tissue. The problem, I believe, is sustaining that effect with drugs like Cyclosporin, potentially toxic drugs which are not innocuous agents. Clearly a lot more work has to be done before this could actually be generally useful in medical practice.

Mr. CONTE. Did you mentioned this can be done also by implantation of insulin-producing cells?

Dr. RENAULT. No, I did not mention that. That is still another strategy—one in which there is a great deal if interest and a great deal of activity currently. Islet cell transplantation, essentially: taking the insulin-producing cells, processing them and then injecting them into or implanting them into a diabetic patient, the cells remaining viable and producing insulin, and essentially correcting the defect in diabetics. In the last year several patients have actually received such implants.

Mr. CONTE. And they have worked?

Dr. RENAULT. They have worked for a period of time, but there were some technical problems. I don't think there are any problems that cannot be overcome, but basically there are two aspects to the problem. The one that has been the most difficult is the site of implantation. The spleen, apparently, was used for most of these implants; and the spleen, it turns out, is probably not a good organ for this. What will probably have to be found is a better site of implantation, but work is going on in that very area. The other aspect of the technology is the purity of the cell preparations that are to be implanted. We do have a very pure preparations now. The great breakthrough here occurred a year or two ago when we were able to identify and actually remove those cells that are responsible for rejection. Clearly that is what is going to push this whole area forward. My understand from Dr. Lacy's reports is that there are still improvements in purity that he would like to achieve and a great deal of work is going on, with private-sector help in trying to devise a better instrument for purifying these cells.

Mr. CONTE. Thank you, Mr. Chairman.

Mr. EARLY. Mr. Hoyer?

ORIGINAL BUDGET REQUEST

Mr. HOYER. Thank you, Mr. Chairman. Dr. Renault, I don't know whether Mr. Early asked you this question or not. Neither he nor I have asked it of previous witnesses. Did he go through what your request was to NIH?

Dr. **Renault**. No, sir.

Mr. **Hoyer**. For 1987. Can you give me that?

Dr. **Renault**. Our request for 1987 is $418,971,000.

Mr. **Hoyer**. No, that's what you got, Doctor. I sometimes find that there is a great difference between what I request and what I get.

Dr. **Renault**. I misunderstood. [Laughter.]

Mr. **Hoyer**. I understand.

Dr. **Renault**. You mean our request to the NIH.

Mr. **Hoyer**. What you thought as opposed to what Mr. Miller thought.

Dr. **Renault**. All right. That was $559,747,000.

Mr. **Hoyer**. Let's go through that transfer, then, to the NIH. What was their request to the Department?

Dr. **Renault**. I don't have that. I have the Department's request to OMB. The Department's request of OMB was $482,940,000.

Mr. **Hoyer**. Dr. Wyngaarden, do you by any chance have NIH's request to the Department?

Dr. **Wyngaarden**. We have the request only for NIH as a whole and by mechanism. At that stage we were not asked for an individual breakdown.

IMPACT OF BUDGET REDUCTIONS

Mr. **Hoyer**. I know. Now, were there any specific items, efforts, objectives that were included in your request of $559 million or, alternatively, the $482 million that are not in the $418 million?

Dr. **Renault**. You mean specific activities that we would not do?

Mr. **Hoyer**. As opposed to just across-the-board reductions for those specific activities that were dropped. If so, can you tell me what those are?

Dr. **Renault**. We did not have to stop doing anything that we were doing. Clearly there are some clinical trials, for example, that we will not be undertaking. There are a number of initiatives that we will not undertake at this budget level. But we have not had to stop doing anything.

Mr. **Hoyer**. What initiatives were they?

Dr. **Renault**. In addition to clinical trials, of which there are five in the planning stage, we also had a great deal of interest from the field to establish a program on kidney centers. We also had some interest in expanding our centers program in diabetes and in the clinical nutrition research units. Clearly we will not undertake any initiatives such as these.

DIABETES CENTERS

Mr. **Hoyer**. Doctor, let me ask you about that. It is my understanding that we have had the same number of centers, which I understand is 14—do we have 14?

Dr. **Renault**. Yes, that is correct.

Mr. **Hoyer**. For the past ten years. Is that correct?

Dr. **Renault**. It sounds correct. I don't have that exact number with me, but I believe it is correct.

Mr. **Hoyer**. Now, as I understand it, when you say expand the centers you mean add to that number.

Dr. **Renault**. Add a few more centers, correct.

Mr. **Hoyer**. How many centers could have been added out of the $482 million?

Dr. **Renault**. I would estimate four or five centers?

Mr. **Hoyer**. Four or five centers?

Dr. **Renault**. Yes.

Mr. **Hoyer**. So a 40 or 50 percent increase in the number of the centers.

Dr. **Renault**. Yes, sir.

Mr. **Hoyer**. Was that recommendation based upon a perceived need for such expansion?

Dr. **Renault**. Yes, there was a perceived need. It was a recommendation made by the National Diabetes Advisory board.

NIH BUDGET LEVELS

Mr. **Hoyer**. Parenthetically, Dr. Wyngaarden, if I can ask you again, as I recall we started out at $6.4 billion for a combined Institutes request.

Dr. **Wyngaarden**. The combined Institutes' request to NIH was $6.5 billion.

Mr. **Hoyer**. $6.5 billion?

Dr. **Wyngaarden**. The Institute's request to the NIH was $6.594 billion.

Mr. **Hoyer**. Yours was $6.4 billion.

Dr. **Wyngaarden**. The NIH request to the Public Health Service was $6.415 billion.

Mr. **Hoyer**. And the Department's was $5.9 billion?

Dr. **Wyngaarden**. The Public Health Service request to the Department was $6.0 billion and then the Department——

Mr. **Hoyer**. I was leaving out the Public Health Service. Now, would I be correct if I extrapolated from that a similar reduction, which was to say about $100 million, from NIH to your overall request to PHS, from $6.5 billion to $6.4 billion?

Dr. **Wyngaarden**. Yes, about $179 million.

Mr. **Hoyer**. Okay. Almost $200 million, then; $6.5 billion to $6.3 billion. Would it be correct to say that that was pretty much across the board?

Dr. **Wyngaarden**. Yes, that is correct.

Mr. **Hoyer**. In other words, what I am saying is could I apply the same percentage to the request for $5.9 billion and come up generally with what your thinking was?

Dr. **Wyngaarden**. I suspect so, although I am not certain. One of the reductions between the Institutes' estimates to NIH and the NIH request to the Public Health Service was in the total number of grants. Whether there was a proportionate reduction in other mechanisms, I am not sure. The Department reduced the number further, I honestly don't know whether there was a proportionate reduction in all those. The largest reduction was in the number of awards. Maybe Mr. Williams could handle that question better.

Mr. **Hoyer**. Mr. Williams, obviously what I am trying to get at is sort of a ball park figure that I can apply to the $559 million, whether that would be 2 percent or 3 percent.

Mr. **Williams**. I think the characterization that one of the key elements in the decision, at least at the Department level, is in the element of the number of research grants. In that sense, the impact would have been roughly across the board with major deviations Institute by Institute.

Dr. **Wyngaarden**. That is true, I think, as far as Institutes are concerned.

DIABETES CONTROL AND COMPLICATIONS TRIAL

Mr. **Conte**. Doctor, will you bring us up to date on the Diabetes Control and Complications Trial.

Dr. **Renault**. We have initiated the full-scale clinical trial this year. That, as you perhaps recall, was the culmination of a lengthy planning process where the study was designed in cooperation with diabetologists around the Nation. And a pilot phase was actually conducted to determine whether or not the trial would be feasible. That pilot phase was evaluated during this last year by two independent review committees looking at it from slightly different points of view. Both committees concluded that the trial not only was feasible, but was very desirable. So we have gone ahead and initiated that trial.

Mr. **Conte**. In light of that, does sequestration have a markedly adverse effect on it? I know it is 4.3 percent across the board. I presume it hit this as well.

Dr. **Renault**. No, it did not affect this trial, per se. We are still in the process of reviewing applications for it, so that the budget is not complete. I would estimate, however, that we might take maybe 5 percent cut from the requested amounts or something on that order, but we feel this is a very high priority initiative and also the sort of thing that is very difficult to reduce support of without endangering its success.

Mr. **Conte**. Can you tell me how much is allocated to that trial in 1987; can you break it out?

Dr. **Renault**. In 1987? Yes. We estimate—and these are estimates—that in 1987 we would spend $17,471,000 on that trial.

Mr. **Conte**. What is the 1986 level, the same?

Dr. **Renault**. No. It is less. It is $14,337,000.

Mr. **Conte**. Mr. Chairman, I believe my time is up.

Mr. **Early**. Before I yield to Mr. O'Brien, Doctor, I want to mention that there was much enthusiasm and excitement about that trial during last year's testimony. Will you provide for the record what you are going to do with that $17,471,000 and tell us if there are reductions what would be cut. Even a 5 percent reduction in something so enthusiastically supported wouldn't be in the right direction.

Dr. **Renault**. Yes.

[Information follows:]

INFORMATION FOR THE RECORD REGARDING
THE DIABETES CONTROL AND COMPLICATIONS TRIAL

In FY 1987, all of the DCCT clinical centers will be actively recruiting volunteers for the study. There are currently about 500 volunteers enrolled in the DCCT and we expect this to increase to approximately 850 by this time next year. There are currently 21 clinical centers participating in the DCCT and four to six new centers will be added in late FY 1986. The addition of these centers was strongly recommended by the two expert advisory groups overseeing the study in order to increase the total number of subjects for the DCCT by 20% to 1400 to provide a margin for errors in the statistical assumptions used to calculate the sample size needed for the study.

This 20% increase in sample size must be accomplished by adding a limited number of new clinics because it is not feasible to expect that the current 21 clinics can recruit and manage more than the 50-55 patients now scheduled for randomization by each center. There is a finite limit to the number of subjects available to be recruited by a single clinic in any given location as well as a limit on the institutional resources a single research project can consume (e.g., space, staff time, hospital and clinic facilities).

Another reason for adding clinics is to improve the geographic distribution of the present DCCT clinics: only one of the DCCT clinics is located west of Dallas, Texas. Further, the original scientific merit review resulted in selection of multiple clinics within close proximity--Massachusetts, 2 clinics; Tennessee, 2 clinics; Minnesota, 3 clinics; Missouri, 2 clinics. Thus, 40 percent of the present DCCT clinics are located in four states, and 95 percent of the U.S. clinics are in the eastern half of the continental United States. Major sections of the country as well as major urban population centers are not being accessed by clinics participating in the DCCT.

Lastly, the addition of centers in selected new sites would alleviate a potentially serious problem for the DCCT: losses to follow-up of patients who relocate during the course of the trial. With the present lack of geographic coverage, the study is in jeopardy of losing subjects who relocate. Additional clinics in major population centers would help to minimize the numbers of patients lost to follow-up over the next seven years.

Unlike many other clinical trials where most of the costs of the trial are concentrated in the period of recruitment, eligibility screening and randomization of volunteers and at the final follow-up examination, the protocol of the DCCT requires active intervention with the volunteers throughout the entire follow up period. Therefore, the costs of conducting the DCCT will continue to increase until all 1400 volunteers are enrolled and are being treated. The costs of the follow up period after the last volunteer is enrolled should remain relatively constant until the final year of the study when the costs will increase again because of the clinical assessments which must be conducted on all of the volunteers at the end of the study.

If reductions from the projected $17,471,000 cost of the DCCT in 1987 are needed, some aspect of the current protocol will have to be changed, i.e., deletion of an assessment or a less frequent assessment of a selected parameter. One aspect that would receive such consideration is the neurology assessment. During the feasibility phase (Phase II) of the DCCT, the National Institute of Neuorological and Communicative Disorders and Stroke (NINCDS) had provided support for what is referred to as the neurologic component of the DCCT. This component included detailed neurologic histories and physical examinations, nerve conduction velocity studies, and an assessment of autonomic nervous system function at baseline (or entry into the study) and every year thereafter. The NINCDS declined to participate in the full scale clinical trial (Phase III) and the NIADDK in conjunction with the DCCT Study Group is considering which aspects of this neurologic component can be retained. A reasonable approach, which would save some money but still provide an assesment of the effect of the two treatment regimens on the development and progression of diabetic neuropathy, is to limit the frequency of the neurologic assessments to baseline, 5-year and end of the study.

Mr. EARLY. Mr. O'Brien.

KIDNEY-UROLOGY CENTERS

Mr. O'BRIEN. Thank you, Mr. Chairman. It is good to have you here, Doctor.

Dr. RENAULT. Thank you.

Mr. O'BRIEN. As probably you know, or possibly you do, I have had a certain particular interest in kidney-urology centers and I note on page 262 of your justification statement a report endorsing the scientific feasibility and appropriateness of such a kidney-urology center's program is being prepared for transmission to the Committee. Has the report been completed?

Dr. RENAULT. We have completed the report, sir, and I believe it has been submitted.

Mr. O'BRIEN. I have not received a copy myself.

Dr. RENAULT. I am not sure it has gotten here yet.

Mr. O'BRIEN. I don't know whether the Committee has, but I would just urge you to see that we get copies.

Mr. EARLY. I would suggest we have not, because the staff had asked me to ask that question.

Mr. O'BRIEN. I see.

Dr. RENAULT. All right. It has not gotten here, but it has left our Institute and it is in process.

Mr. EARLY. We have it now.

Mr. O'BRIEN. We do have it? I see. Well, good. I take it from the way your statement and the justification reads that the report endorses the feasibility of the centers' concept. Is that correct?

Dr. RENAULT. Yes.

Mr. O'BRIEN. Do you have any highlights you might touch on for us?

Dr. RENAULT. The centers mechanism and program project grants allow us to provide resources for a group of investigators working together to focus on a given problem. In the area of kidney and urologic diseases, I think we have identified some areas that we feel could benefit from a multidisciplinary approach. For example, hypertension and the kidney; diabetes and kidney; obstructive and heredity diseases of the urinary tract and the kidney, such as the polycistic kidney disease; nutrition and the kidney; immunology and the kidney (immunologic abnormalities are among the greatest causes of kidney disease such as glomerlonephritis); and finally, trauma and damage to the kidney.

Mr. O'BRIEN. I might just mention, parenthetically, I have a close person friend, a constituent, who is very much interested and very supportive into kidney disease: Mr. Harold Schwartz of Chicago. I wonder if I could get an extra copy of the report that I could give to him.

Dr. RENAULT. Of course.

NIH CLINICAL CENTER

Mr. O'BRIEN. There is one other thing I would like to touch upon which I have asked several of the other heads of Institutes. You are now a member of the medical staff of the Clinical Center, National Institutes. Is that correct?

Dr. RENAULT. Yes, I am.

Mr. O'BRIEN. It appears to me that in the clinical center we are handicapped more for lack of staff than any other particular shortcoming. I have spent a little time out there and it seemed to me there is a reduction in, or lack of, sufficient staff. Your staff, I think, is excellent. You work very hard. Maybe if we whomped up some more money for you, you would be able to do more. Is that a fair comment?

Dr. RENAULT. I am not sure I am the most qualified to speak about the situation in the clinical center. I think from our Institute's perspective I certainly agree that the clinical center has been an outstanding resource for us in pursuing clinical research, particularly in liver disease and kidney disease, in lupus nephritis and in peptic ulcer disease. We have been talking with the clinical center director about cutbacks, cutting back in the amount of space: say, closing some wards. It has certainly been in consideration.

Mr. O'BRIEN. Is that because you don't have a sufficient number of full-time equivalents? I would hate to be known as a "full-time equivalent."

Dr. RENAULT. Right.

Mr. O'BRIEN. Is there a better term than that?

Dr. RENAULT. Maybe I could turn to Dr. Wyngaarden. I believe that that may play a role. I think there are many factors. I think it is a very complex problem in managing that kind of a hospital. It is essentially a research hospital which does not have a primary service base.

Mr. O'BRIEN. But if we were able to whomp up some additional full-time equivalents, Dr. Wyngaarden, I suspect you would be using them.

Dr. WYNGAARDEN. Yes, sir. The immediate stimulus for considering the collapsing of the wards together is to save personnel costs.

Mr. O'BRIEN. I see.

Dr. WYNGAARDEN. When we have two more or less adjacent or equivalent wards operating there——

Mr. O'BRIEN. Forgive me for interrupting. When you collapse wards together, that means there are fewer patient beds available for patients who need your care.

Dr. WYNGAARDEN. That is right. There would be fewer patient beds available. However, when there are two wards with each having a 35-percent census, there would be some merit in combining them. The longer-range stimulus for this consideration is the budget. The Clinical Center expenses are somewhat on the same order as teaching-hospital expenses: they run ahead of inflation. We have to consider that in long-range planning.

Mr. O'BRIEN. Thank you, Doctor. Thank you, Mr. Chairman.

COOPERATIVE STUDIES WITH HCFA

Mr. EARLY. Now, what is the current status of your cooperative study with the HCFA with regard to kidney disease?

Dr. RENAULT. Well, we feel that that has been a particularly successful venture for us. It is a new area of cooperation for our Institute. Essentially what we have been able to negotiate that the NIH will support the research costs of doing this clinical trial, which is to study the effect of nutrition and a couple of other nutritionally-related interventions in chronic kidney disease to see if we can prevent the progression of chronic kidney diseases. The Health Care Financing Administration has agreed to support the clinical costs, and those are substantial.

Mr. EARLY. Would you, for the record, expand on that?

Dr. RENAULT. Certainly.

[Information follows:]

STATUS OF COOPERATIVE STUDIES WITH HCFA

There have been two important events in cooperative studies between the NIH and the HCFA in the area of renal disease. The first is that related to prevention of end-stage renal disease. Based on P.L. 92-603 we jointly developed a clinical trial to evaluate the efficacy of dietary intervention in the modification of progress of renal disease. In this trial, each bureau is responsible for that part for which it is most qualified, namely, NIH conducts the scientific and medical aspects and HCFA oversees and supports the patient care costs. In theory, both agencies can thus profit maximally from this type of arrangement. In fact, this has turned out to be the case during the first part of the study which has first been completed. We believe that this represents a good model for the best use of scarce resources, especially at this time of fiscal restraint.

We have extended this thinking to begin sharing data on the causes and costs of renal failure. In November 1985, Bureau of Data Management and Strategy/HCFA, and NIDDK signed an agreement to develop a registry of end-stage renal disease. This data base will provide a critical piece of missing information on the causes, complications and costs of end-stage renal disease. Both agencies believe this data is essential to future planning for research and patient care.

LITHOTRIPTOR

Mr. EARLY. Doctor, how effective is the lithotriptor turning out to be, as a treatment method for kidney stones?

Dr. RENAULT. Well, it seems to be quite effective. It certainly has been used a great deal and I think increasingly so. To date, I have not really heard anything negative about it in terms of its not being effective.

Mr. EARLY. Thank you, Doctor. Can you tell us anything about what the Department of Defense is doing on their Star Wars initiative with the lithotriptor people?

Dr. RENAULT. Are they? I am not aware of that, sir.

GALLSTONES

Mr. EARLY. I was told that they were going to spend money for that specific treatment. What progress has been made in the prevention and treatment of gallstones without surgery?

Dr. RENAULT. Here we have an interesting development, which is an ether compound. It is methyltertiary butyl ether, which can actually dissolve gallstones. It is, of course, very experimental; but it is very interesting and potentially very useful. What is done is a needle is put through the skin into the liver and into the gall bladder and the ether is injected into the bile to dissolve the stones. Of course, if this could be successful and made generally available, it would have a tremendous impact on surgery rates and costs, and morbidity in suffering for individuals. I think this also is a very important issue for the aging because, clearly, the incidence of gallstones and inflammation of the gall bladder increases with age and surgery is very often very difficult for elderly people.

Mr. **Early**. It does sound encouraging. Doctor, before we excuse you, I just want to tell you we have numerous questions that we are going to submit for the record.

Dr. **Renault**. Yes.

Mr. **Early**. If you would supply the answers, we would appreciate it.

PROSTATIC DISEASE

A final question. Doctor, most men over 60 have prostate problems. What can you tell us about the current status of research on the prevention and treatment of prostate conditions?

Dr. **Renault**. I don't think that, unfortunately, that picture has changed very much in either the prevention or the treatment. What I can report that is most encouraging, I feel, is that we have been able to interest several investigators skilled in male hormone research—I believe we have six applications to study male hormone receptors in the prostate gland; male hormones are probably responsible for the growth of that gland. We really need this kind of research to understand the factors which govern the growth of the prostate and ultimately develop a non-surgical approach to treatment.

Mr. **Early**. Please supply for the record what the current status of the growth hormone therapy is.

Dr. **Renault**. We will.

[Information follows:]

Hormone Therapy on Prostatic Disease

There has been a resurgence of scientific interest in prostatic diseases and on hormone therapy leading to the following discoveries:

Prostatic stromal tissue capable of inducing growth of the prostate has a greater amount of nuclear androgen (dihydrotestosterone) receptor than does prostatic epithelial nuclei.

The nuclei of tissue taken from patients with Benign Prostatic Hyperplasia have higher concentrations of androgen receptors (dihydrotestosterone) than nuclei taken from normal prostates, whereas, total prostate gland contents of androgen are the same for BPH and normal glands.

Benign Prostatic Hyperplasia tissue shows a significant reduction in the ability to convert the androgen (dihydrotestosterone) responsible for abnormal prostatic growth to a biologically inactive form when compared to normal prostatic tissue.

A major proportion of steroid (a hormone) capacity of nuclei from prostate tissue is contained in the nuclear matrix which also serves to anchor DNA sequences and RNA processing.

Both tissue and prostatic secretions may contain a growth factor capable of inducing growth in the prostate gland.

This recent progress points to the increased awareness in the scientific community of prostatic diseases. The strong legislative and administrative support of urologic research through the centers program will foster and continue this needed focus of research emphasis.

Mr. **Early**. Doctor, we want to thank you for your testimony.

Dr. **Renault**. Thank you very much, sir.

[The following questions were submitted to be answered for the record:]

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scale trial. The cost of completion of the full-scale clinical trial is estimated to be $133 million. The total cost for this study, including the costs for the feasibility study, is estimated to be $153 million. It is anticipated that at least $5 million of the total cost will be contributed by the private sector in the form of donated products for use in the trial, e.g., insulin and syringes.

Mr. Conte. Is provision made for this trial in the budget you present to us?

Dr. Renault. Yes. The President's budget for FY 1987 provides $17.145 million for the Diabetes Control and Complications Trial.

DIABETES CENTERS

Mr. Conte. Now, as I understand it, you have an application before you for a new center in diabetes, which has been recommended highly by the Advisory Council, but for which it is unclear whether sufficient funding is available. Can you please describe what the circumstances are here, and what the chances of this application are to be funded?

Dr. Renault. I believe you may be referring to a new grant application from the Joslin Diabetes Center in Boston. This application, which was submitted to NIH in 1985, was subsequently reviewed for scientific and technical merit by a site visit team of expert consultants which recommended approval of the application with very high enthusiasm. Very recently, our Institute's National Advisory Council concurred with this recommendation for approval, and the application can now be considered by the Institute for award. At the present time, however, there are two additional diabetes center applications that have not yet completed the peer review process but which are also competing for support from FY 1986 funds. In contrast, the Joslin request is a new application for support as a Diabetes and Endocrinology Research Center. The Institute's current budget does not provide for any expansion of the total number of diabetes centers supported, and therefore, only two of these three applications can be funded during FY 1986. It is unlikely that we will be able to make a decision regarding the possibility of an award for the Joslin application until our National Advisory Council has completed its review of both of the other competing applications on September 25, 1986. If an award is not made for the Joslin application this year, it will remain in competition for support during FY 1987. At that time, we expect to receive four additional renewal aapplications for diabetes centers, and the Joslin application would again have the opportunity to compete for support.

DIGESTIVE DISEASES

Mr. Conte: What do you have to report in the area of Digestive Diseases? Anything of interest you want to tell us about?

Dr. Renault: There are a number of areas of digestive diseases science that are exciting and worthy of reporting. Among

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ISLET CELL TRANSPLANTATION

Mr. Conte. How about the implantation of insulin-producing cells -- what is happening there, and will you end up with an increase in funding to try to intensify work in this area, or does Gramm-Rudman-Hollings take care of that initiative?

Dr. Renault. During the past year, there has been very significant progress in research related to transplantation of insulin-producing pancreatic islet cells. These advances have reached the point that centers in St. Louis, Miami, and Minneapolis have now initiated clinical studies involving islet transplants in patients with advanced diabetes who require immunosuppression for maintenance of kidney grafts. These initial studies have clearly demonstrated partial graft function in the majority of islet transplant recipients. Although none of the recipients have yet become totally insulin-dependent, two of the grafts are still functioning at seven months post transplant. In addition, various technical refinements have been made in the procedures for isolation of human islet cells from the whole pancreas which greatly improve the purity of the transplant preparation. This purified islet cell preparation has also been used very recently in experimental animals to assess the feasibility of transplanting islet cells directly into the liver. At this time, clinical studies are being initiated to assess this site of implantation in the human. Additional clinical and preclinical studies involving differentiated and undifferentiated islet cell transplants are also underway in Dallas, Denver, New York, Philadelphia, and at various other research centers throughout the United States. These studies will involve efforts to further improve the quality and quantity of islet tissue for transplantation, to define the effects of immunosuppression on islet engraftment and function, and to facilitate procurement and preservation of both the pancreas and isolated islets. Under the President's budget for FY 1987, we will continue to support the most meritorious investigator-initiated studies in this high priority area of diabetes related research. However, we will defer support for a major expansion of resources in this area until further progress demonstrates clearly that this would be appropriate.

DIABETES CONTROL AND COMPLICATIONS TRIAL

Mr. Conte. Last year, I believe, at this time, the Institute was conducting its analysis of the feasibility phase of the very large Diabetes Control and Complications Trial, to show whether close control of blood sugar was helpful in avoiding or slowing down the harmful side effects of diabetes. Have you made a decision as to whether to mount the full scale clinical trial, and if so, what do you estimate the cost will be?

Dr. Renault. Analyses of the feasibility data from the DCCT were completed in May. Independent assessments of these data were provided by two groups of expert advisors selected on the basis of their expertise and because they had no involvement in the conduct of the trial. Both groups found that by all essential criteria, the feasibility objectives had been met and they enthusiastically recommended that the trial proceed. Based on these recommendations, the NIADDK announced its decision to proceed with the full-

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these are the research areas of gut motility, gut-brain peptides, gut immunology and diarrheal disease; a liver transplant data system, and the procurement of human liver tissue for research; nutritional research opportunities involving fatty acids; and the use of methyl-tertiarybutyl-ether (MTBE) in dissolving gallstones.

There have been significant improvements in our understanding of intestinal motility and how it is controlled. For example, disorder experienced by many people is "heartburn." For most people, this is an innocuous and temporary condition associated with overindulgence of food and drink (or both). It is a consequence of the reflux of acidic stomach contents back into the esophagus. This causes irritation, and in severe cases erosion, of the esophageal lining. The lower esophageal sphincter, at the junction between the esophagus and the stomach, normally prevents the stomach contents from entering the esophagus. Research on the control of this sphincter has led to the discovery of several naturally occurring substances which help to regulate the amount of tension exerted by this muscle. Such knowledge of the basic mechanisms controlling this sphincter may lead to new treatment of both mild reflux problems and the more debilitating chronic disorders which can result from severe reflux problems. Equally important, these studies will contribute to the understanding of the integrated motility of the entire digestive tract, and ultimately to the management of many other disorders.

Digestive diseases research of important clinical implications includes the study of small proteins, called peptides, which regulate many gut functions. Interestingly, these regulatory peptides are found in both the brain and gut, and in some cases may prove to have related actions, integrating gut and brain functions. Cholecystokinin (CCK) is one such regulatory peptide, with specific roles in the proper functioning of the gut in digestion of food, especially fat and protein. As food moves from the stomach and into the small intestine, CCK is released from the gut. This release of gut CCK is involved in the signalling to the gallbladder to contract and release bile, and to the pancreas to secrete digestive enzymes, into the small intestine. The signaling from the gut to the brain that one has eaten sufficiently also releases the same substance, CCK, at the brain. Brain CCK is implicated in satiety. Knowledge of the action of gut and brain CCK allows inquiry into disorders of production and release of CCK. From such inquiries, new approaches to treatment of digestive and eating disorders may emerge. Thus, new treatments may result from better understanding the relationship between improper gallbladder emptying and gallstone formation, and from the relationship between the urge to over-eat and some types of obesity.

Diarrhea from infectious causes still contributes considerably to neonatal and infantile morbidity and mortality in much of the world; moreover, acute diarrheal disease is a major cause for loss of productivity in Western societies. Chronic diarrheal diseases, often manifested as states of intestinal malabsorption, though less common, are important because of their long-term morbidity in the young. It has recently become clear that a number of infectious diseases of the gastrointestinal tract are mediated by attachment of microorganisms and toxins to the intestinal mucosal surface of the host. Evidence suggests that, in each case, 82Ap

mucosal adherence is mediated by a specific "binding site"-"receptor site" interaction between surface structures elaborated by bacteria and naturally occurring elements of the host mucosal surface, respectively. Rapid progress has been made in localizing these colonization factor antigens. In contrast, very little progress has been made in defining the specific receptors on the intestinal surface of the host which mediate adherence. Work needs to be done in defining the mucosal receptors for enterotoxins, bacteria, viruses, and protozoa. For example, investigations are needed addressing questions such as: 'Do these receptors share other important digestive or absorptive functions?' and 'At what age do they develop and what is their distribution in the host?' The NIDDK, in collaboration with other institutes, will encourage the expansion of studies in this area.

Remarkable progress has been made in the area of liver transplantation, offering the new hope of life to many people whose conditions would otherwise be considered beyond help. Many major questions associated with liver transplantation, and liver diseases in general, however, remain unanswered. An important opportunity to study diseased and healthy human liver emerged in association with liver-transplant technology. The NIDDK has established a liver transplantation data system at the University of Pittsburgh. This system will enable collection, analysis, and interpretation of the data resulting from liver transplant experience from many hospitals across the country. Such information will be invaluable to understanding questions such as who is most likely to benefit from liver transplantation, and what emerging techniques are the most useful.

The diseased livers removed from patients at the time of transplant, and normal donor livers which for certain reasons cannot be used as planned in a transplant, are important objects for research. The NIDDK has planned for a liver procurement and distribution system, to be supported by contract, to take advantage of this research opportunity.

Research progress on the effects of omega-3 polyunsaturated fatty acids derived from seafoods was reviewed at a recent conference on Health Effects of Polyunsaturated Fatty Acids in Seafoods. Information presented at the conference clearly indicated the important role of omega-3 fatty acids in the modulation of human metabolism, and their potential role in the prevention and treatment of a number of important diseases. These diseases include cardiovascular diseases, cancer, asthma, certain forms of arthritis, and inflammatory and autoimmune processes. The NIDDK has collaborated with several other institutes to encourage grant applications to pursue research opportunities on this important topic.

Gallstone disease and treatment contributes markedly to the total health care costs of the Nation. A major portion of this cost is due to the lengthy recuperation in the hospital and home following gallstone surgery. Years of study, with numerous chemicals, have been devoted to attempts to dissolve gallstones within the gallbladder or ducts as a way of circumventing the trauma of gallstone surgery. This goal is nearer reality with current studies of gallstone dissolution using methyl-tertiary-

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butyl-ether (MTBE). The technique involves the positioning of a catheter, through the skin and liver, into the gallbladder. The MTBE is then introduced into, and withdrawn from the gallbladder via this catheter. Many important research questions remain to be addressed of this type of treatment. For example, what will be the recurrence rate of stones so treated, and how often can a patient be treated for stones using this technique? Such questions, and the more important question of gallstone prevention, are being aggressively pursued by the Institute.

DIGESTIVE DISEASE CENTERS

Mr. Conte: What is the status of the digestive diseases centers program? Are they fully funded under the budget proposal?

Dr. Renault. The newly expanded digestive diseases research center program in NIDDK supports 12 research centers located throughout the United States. The following table provides information about each center.

Principal Investigator	Location	Research Focus	Budget Year	End Date
Dr. J. Boyer	Yale University	Liver Disease	2	8/31/89
Dr. W. Silen	Harvard University	GI Structure & Function	2	8/31/89
Dr. J. Christensen	University of Iowa	GI Motility	2	8/31/89
Dr. D. Powell	University of North Carolina	Diarrheal Diseases	1	8/31/90
Dr. T. Yamada	University of Michigan	GI Hormones	2	11/30/89
Dr. S. Phillips	Mayo Foundation	GI Physiology & Secretion	2	11/30/89
Dr. M. Donowitz	Tufts/New England Med Center	GI Absorption & Secretion	1	11/30/89
Dr. J. Bloomer	University of Minnesota	Liver Disorders	1	8/30/90
Dr. F. Simon	University of Colorado	Liver Diseases	1	8/30/90
Dr. W. Snape	University of California Harbor Med. Center	Inflammatory Bowel Disease	1	7/31/90

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Dr. R. Ockner	University of California, San Francisco	Liver Diseases	7	6/30/90
Dr. D. Schafritz	Albert Einstein Medical Center	Liver Diseases	13	5/31/87

The digestive diseases research centers are not fully funded to the amounts recommended by peer review study sections. In FY 1986 center budgets are to be reduced by 13 percent. Comparative reductions in 1984 and 1985 were six percent and four percent. In FY 87 the proposed budget plan reduces center funding by 20 percent.

Mr. Conte. What is the average reduction from full commitment levels that you are estimating under the post-sequester budget, the revised 1986 budget assuming rescission, and the proposed FY 1987 budget?

Dr. Renault. We estimate reduction in our centers program of thirteen percent at either of the 1986 budget levels and of twenty percent under the proposed 1987 budget compared with six percent in 1984 and four percent in 1985.

Mr. Conte. For the record, will you provide a list of Digestive Disease Research Centers, and indicate which were funded in FY 1984 and which were funded in FY 1985?

Dr. Renault. A list of our digestive diseases centers for 1984 and 1985 and their respective funding levels follows:

Digestive Disease Centers
(amounts in thousands)

		1984	1985
University of California San Francisco, CA	Dr. Ochner	$689	$745
Yeshiva University New York City, NY	Dr. Shafritz	$1,308	$967
Beth Israel Hospital Boston, MA	Dr. Silen	$680	$698
University of Colorado Boulder, CO	Dr. Simon	---	$413
New England Medical Center Boston, MA	Dr. Donowitz	$738	$387
University of Minnesota Minneapolis, MN	Dr. Bloomer	---	$632
University of Michigan Ann Arbor, MI	Dr. Yamada	$579	$145

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University of Iowa Iowa City, IO	Dr. Christensen	$534	$628
University of North Carolina Chapel Hill, NC	Dr. Powell	---	$667
Mayo Foundation Rochester, MN	Dr. Phillips	$877	$273
Yale University New Haven, CT	Dr. Boyer	$692	$705
Harbor General - UCLA Medical Center Los Angeles, CA	Dr. Snape	---	$924
	Total	$6,097	$7,184

HEALTH RESEARCH EXTENSION ACT OF 1985

Mr. Conte. Were there any other requirements or provisions of the reauthorization statute affecting your Institute that we should be aware of?

Dr. Renault. Public Law 99-158 provides, in statute, parallel, though not always uniform, authorities for each of the three divisions of the NIDDK. These authorities include information clearinghouses and data systems, interagency coordinating committees, research and training centers, national advisory boards, division directors, and council subcommittees. The Law also requires the Secretary to conduct an administrative review of the disease research programs of the NIDDK to determine whether any of its programs can be more effectively and efficiently managed by other national research institutes. The Secretary must complete this review within one year of the law's enactment.

RESEARCH GRANT NUMBERS AND AWARD RATES

Mr. Conte. What is the comparable number of new and competing grants that NIDDK funded in FY 1985, and how many will you fund in the sequestered FY 1986 budget, the revised '86 budget, assuming rescissions, and the proposed FY 1987 budget?

Dr. Renault. In 1985, we supported 596 new and recompeting research grants. In 1986, the number would be 637 both before and after sequestration, and 564 after the proposed rescission. In 1987, the number will be 566.

Mr. Conte. What is the award rate, the number of scientifically meritorious grant applications that you will be able to fund, for NIDDK in FY 1985, the revised '86 budget assuming rescissions, and the proposed FY 1987 budget?

Dr. Renault. In 1985, the award rate was 36 percent. In 1986, under the revised budget we estimate an award rate of 31 percent and in 1987 the estimate will be 30 percent.

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DOWNWARD NEGOTIATIONS

Mr. Conte. What downward negotiations from the full commitment level are you assuming in your new and competing grants, your continuation grants, your centers, and your other mechanisms for FY 1986 and FY 1987?

Dr. Renault. In 1986, under the revised budget, we will negotiate grants downward about 10 percent and centers 13 percent. In 1987, the estimates are 12 percent and 20 percent respectively.

Mr. Conte. How does this compare with your historical levels of downward negotiations?

Dr. Renault. In 1984 and 1985 we reduced grants an average of 4 percent. We reduced centers 6 percent and 4 percent in those years.

NEW ARTHRITIS INSTITUTE

Mr. Conte. What was your level of FTEs in FY 1985 when the institute included the arthritis section, and what will it be in FY 1987 under the budget?

Dr. Renault. In 1985, the FTEs for the combined NIDDK and NIAMSD were 674. In 1987, the combined total will be 648.

Mr. Conte. What happens to the size of your intramural program under the reorganization?

Dr. Renault. The reorganization itself had no real impact on the intramural program, however, most of the FTE reduction will have to be made in the intramural program since we believe that we are already at minimum levels needed to fulfill our management and statutory responsibilities.

Mr. Conte. What about office space and facilities after the reorganization? Any problems?

Dr. Renault. We believe the current space and facilities are adequate for the current staff.

CLINICAL TRIALS

Mr. Conte. On clinical trials, will the revised budget for '86 and the proposed budget for FY 1987 require cutbacks from planned levels of commitment for any ongoing clinical trials?

Dr. Renault. Most of our clinical trials are carried out through research grants and except for the Diabetes Control and Complications Trial and the trial on Modification of Diet in Renal Disease which will be partially protected to maintain the integrity of these studies, most of our other clinical trials will be reduced along with other grants by about 10 percent in 1986 and 14 percent in 1987.

Mr. Conte. Are there any clinical trials that are ready to go that will not be funded under the proposals for FY 1986 and FY 1987?

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Dr. Renault. Yes, there are at six planned clinical trials which will not be initiated in either 1986 or in 1987. A list of them follows:

Additional NIDDK Clinical Trials Which Could be Initiated in 1987

	Estimated Costs ($ in thousands)	
	FY 1987	Total
o Treatment of Short Stature with Human Growth Hormone. A clinical trial has been proposed to study the safety and efficacy of biosynthetic growth hormone with and without oxandrolone in treating children with short stature not due to growth hormone deficiency.	$420	$1,400
o Nonsurgical (Balloons) Reduction of Stomach Capacity in the Treatment of Morbid Obesity. Balloon therapy for reducing stomach capacity may be an effective method for treating morbid obesity which could avoid surgery and its inherent risks. The Digestive Diseases and Nutrition Subcouncil of the National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council has recommended that a request for applications be issued for a clinical trial to test the safety and efficacy of balloon therapy for morbid obesity.	$212	$464
o Postoperative Decompression Feeding Trial. A multicenter clinical trial of early postoperative bowel decompression and feeding has been proposed. This would test a variety of interventions, with the goal of reducing the duration of postoperative hospital stays, in approximately 600 surgical patients.	$4,785	$25,500
o Kidney Transplantation in Children with ESRD. A clinical trial to determine the optimal protocol for kidney transplantation for children with end-stage renal disease has been proposed.	$250	$1,000
o Expanded Nephrologic Component of the	$480	$6,650

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DCCT.

If additional funds were made available, consideration would be given to funding an expanded nephrologic component of the Diabetes Control and Complications Trial (DCCT) which would test the benefit of early intensive treatment of insulin-dependent diabetes mellitus on the development and progression of diabetic nephropathy. This complication of diabetes accounts for approximately one-fourth of the new cases of end-stage renal disease in the United States each year.

o Controlled Clinical Trial of Hematin Therapy for Acute Porphyric Attacks.	$450	$2,500

A multicenter, controlled clinical trial of hematin, an orphan drug, would attempt to determine the optimum dosage and timing of administration to prevent acute porphyric attacks. Approximately 150 patients would be randomized to hematin therapy or glucose infusion (the current therapy). Adverse effects of hematin on hemostasis would be monitored.

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DIABETES IN MINORITY POPULATIONS

Mr. Roybal. In the Task Force Report on Minority Health completed by the Department of Health and Human Services, diabetes was included as one of the most important contributors to excess mortality in minorities. Do we know how much of this problem can be attributed to genetics and how much to other factors, such as access to care or income for purchase of medication? For instance, another study done by the Department suggests that minorities receive far fewer office visits for this problem than do Whites.

Dr. Renault. The DHHS Task Force Report on Black and Minority Health, to which our NIADDK staff were contributors, should serve as a landmark document, and our Institute is carefully considering the findings and recommendations on diabetes, which was identified as one of the six major contributors to excess mortality This excess was not found for all minorities, but did appear to occur among Blacks, Hispanics, and American Indians. I am not surprised that these three groups were so identified, for we know that diabetes is more prevalent in these groups than in the general population of the U.S. For example, among adults, diabetes in Black Americans is about 60 percent more prevalent than in Whites; the rate in Hispanics is similarly excessive; and some American Indian tribes have among the highest rates of diabetes in the world. This difference in prevalence between these population groups and Whites, which may be attributed to genetics but is certainly also associated with obesity in these populations, may be the major reason for the discrepancy in mortality.

Some factors appear not to be sources of the differential. For example, the National Center for Health Statistics reports that the office visit rate for diabetes was the same for Blacks as for the U.S. population as a whole. The NCHS also reports that in the area of medical care, 2.5 percent of physician visits by Blacks are for diabetes, whereas the rate in the general population is only 1.7 percent. The hospitalization rate for Black diabetics is about twice that for White diabetics. The use of insulin and oral antidiabetic agents for treatment of diabetes is approximately the same in Blacks and Whites. Each of these indicate that Blacks have access to medical care for their diabetes and can acquire medications for diabetes treatment. We do not have as much information about Hispanic diabetics, but we hope to develop new data on this population from the recently completed NCHS Hispanic Health and Nutrition Examination Survey, the diabetes component of which was sponsored by NIADDK. In regard to American Indians, I would defer to my colleagues in the Indian Health Service for information on health care of this segment of the U.S. population.

Mr. Roybal. Is there a need to do an educational effort like we did with minorities and high blood pressure, to push early diagnosis and the importance of maintaining treatment? How much money do you estimate that effort would cost?

Dr. Renault. There is a pressing need for an educational effort directed toward minorities that stresses early detection and treatment maintenance. In the United States, rates of noninsulin-dependent diabetes (NIDDM) are high among Black Americans, Mexican Americans, and American Indians. Black Americans have a 50 percent

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greater prevelance of diabetes than Whites; a startling 50 percent of Pima Indians over age 35 have diabetes; and about 10-12 percent of Mexican American adults have diabetes. The complications resulting from diabetes are both devastating to the patient and a tremendous drain on the economy. Diabetes is the leading cause of new cases of blindness in people aged 20 to 74, years but fewer than half of all diabetic patients are examined each year for diabetic retinopathy. Half of all people with diabetes also have a medical history of hypertension, but only two-thirds of them have adequately controlled blood pressures. After 20 years of diabetes, almost half of all patients have peripheral vascular diseases. In people with diabetes, cardiovascular disease is the primary cause of death. The lowest estimate of costs that are directly attributable to diabetes are approximately $14 billion annually, about 3.6 percent of the total health costs in the United States. Approximately 75 percent of people with NIDDM are obese. By preventing obesity, it is possible that the incidence of NIDDM can be reduced by up to 50 percent. An educational effort directed particularly at people with NIDDM , if successful, would result in a considerable reduction in complications and a concommittant enormous savings to the economy. An effort similar to the NHLBI Hypertension Program would cost approximately $10-15 million per year.

Mr. Roybal. Is the Institute currently funding any education and demonstration programs for diabetes which are targeted to the minority groups? How would those programs be affected by the 1986 and 1987 budget proposals?

Dr. Renault. The Institute is not currently funding any diabetes education or demonstration programs that are targeted to minority groups.

Mr. Roybal. What portion of the NIDDK funding was devoted to research on noninsulin diabetes in general and to diabetes in minorities, in particular in 1985, and what portion will be devoted to the areas in 1986 and 1987? For the record, please indicate the funding level by project type.

Dr. Renault. During FY 1985, NIADDK obligated $104.0 million on projects related to diabetes mellitus and its complications, including $66.5 million for research project grants, $14.0 for research center grants, $1.9 million for research career awards, $5.0 million for National Research Service Award training grants and fellowships, $4.5 million for research and development contracts, and $8.6 million for intramural laboratory and clinical research. Therefore, a total of 19.3 percent of overall NIADDK funding was related to diabetes and its complications. Although the majority of these studies are related at least in part to noninsulin-dependent diabetes, a precise estimate of the associated costs is not available. With respect to NIADDK funding for research involving diabetes in minorities, the Institute supported such studies through both extramural research grants ($1.1 million) and intramural research projects ($3.1 million). Therefore, overall NIADDK funding for these specific activities during FY 1985 totaled $4.2 million, or approximately 0.8 percent of the total Institute budget. However, inasmuch as noninsulin-dependent diabetes presents a disproportionately large health burden to

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minority populations, particularly Blacks, Hispanics, and American Indians, all Institute resources which are devoted to research related to this disease and its complications can be expected to be of major benefit to these minority groups. With respect to future support, we expect that approximately an equivalent proportion of the NIDDK's total resources will be devoted to such studies in FY 1986 and FY 1987 as during FY 1985.

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MINORITY HEALTH ISSUES

Mr. Stokes. Former Secretary Margaret Heckler's Task Force on Black and Minority Health found that diabetes is a major cause of excess deaths among minorities. What will your Institute do differently this year in order to respond to the recommendations of the Task Force?

Dr. Renault: A number of initiatives will be undertaken this year in an attempt to address those disease areas that disproportionately affect minority populations. First, NIDDK plans to study the natural history and pathogenesis of renal disease in the Pima Indian population which suffers from an extremely high incidence of noninsulin-dependent diabetes mellitus. We also plan to formulate treatment plans and conduct clinical trials to prevent the development and progression of renal disease in this patient population. Detailed clinical observations and analyses of renal function, as well as epidemiologic and pathologic investigations, should give insight into the relative importance of glomerular hyperfiltration, hypertension, and control of blood glucose levels in the etiology of disease. In addition, other scientific studies are being conducted on this population by the intramural program of the NIDDK. These studies include assessment of several metabolic parameters and the serum levels of various lipids. A clinical trial will also be designed to evaluate the effects of diet on the progression of diabetic nephropathy in this Indian population.

Second, the Institute has held preliminary discussions on enhancing the continuing medical education of its members regarding the diagnosis and management of diabetes. As noted by the Task Force, Blacks, particularly Black females, suffer from increased risk of noninsulin-dependent diabetes.

Third, NIDDK and the National Coalition of Hispanic Mental Health and Human Services Organization (COSSMHO) will cosponsor several workshops at the upcoming National Hispanic Conference on Health and Human Services, September 4-7, 1986. These workshops will focus on the epidemiology of noninsulin-dependent diabetes in Hispanic populations, as well as the development of an education program for physicians and methods of teaching professionals and patients about noninsulin-dependent diabetes mellitus.

Fourth, NIDDK, through its National Diabetes Information Clearinghouse, is participating in an effort to make a bibliography of Spanish-language materials on diabetes more useful for its intended audience.

Lastly, NIDDK staff have notified the Centers for Disease Control (CDC) of the possible impact on the Hispanic population of diabetes projects, including education programs, that are supported by the CDC in 20 states. This effort may make possible the tailoring of these projects to the special needs of the Hispanic population in those states where Hispanics have a significant presence.

Mr. Stokes. Your FY 1987 budget request is nearly $14 million below the FY 1985 appropriation for your Institute. How

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can you adequately respond to the need to place more emphasis on minority health status with a budget that is declining in absolute and real terms?

Dr. Renault. A declining budget offers us the challenge of maximizing available resources so that these can be applied to full efficiency in all areas of support, including minority health programs. This approach will be a major goal for this Institute in implementing its minority health initiatives.

Mr. Stokes. Diabetes affects about 1 in 20 Americans. We seem to be managing the disease better, in terms of improved treatment methods, but what progress is being made in terms of prevention?

Dr. Renault. For Type I diabetes (insulin-dependent diabetes or IDDM), we are actively pursuing several promising research advances with the potential for developing preventive strategies. These areas include the linkage of diabetic and immune genetics, the nature of the immune response underlying the development of Type I diabetes, and immunosuppression as a potential method of treating newly-diagnosed Type I diabetes.

In recent years, insulin-dependent diabetes has been shown to be linked genetically with certain cellular antigens called the HLA antigens (for histo-compatibility locus antigens). There are five subgroups of these HLA antigens and two subtypes of the DR subgroup, HLA DR3 and HLA DR4, which are present in more than 90 percent of all individuals with insulin-dependent diabetes. HLA antigens are important in determining the immune response of the body. Since recent advances have shown that there are alterations in the immune response in insulin-dependent diabetes, this genetic association of Type I diabetes with HLA DR3 and DR4, when elucidated, may provide a mechanism for identification and intervention of risk for Type I diabetes.

Another aspect of immunity and Type I diabetes is the finding that at the onset of diabetes, almost all patients have antibodies against the islet cells of the pancreas that are produced several years before the development of clinical diabetes and may be the key to identifying those individuals who will actually develop insulin dependent diabetes. A specific protein of molecular weight 64,000 has been identified that appears to be the target for islet cell antibodies. We do not know how these antibodies develop. They may appear following a mumps infection or following a viral infection. We do not know whether viruses play a direct or indirect role in the onset of Type I diabetes.

These and other detailed aspects of genetics and immunity are being investigated in the BB/W diabetic rat, a model for Type I diabetes. This model makes possible studies of genetic linkage and immune alterations that are impossible to pursue in detail in a human population. These studies include immune autoregulation, alterations in islet cell physiology, mechanisms of beta cell injury, islet transplantation, and immunosuppression. In addition, techniques for prevention can be explored with the rat model. Ongoing studies are examining the role of immunosuppressive drugs and of early insulin treatment in preventing the development of

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diabetes in these genetically prone animals. These studies have led to the first trials of immunosuppressive therapy in children with newly diagnosed diabetes.

Unfortunately, we still know relatively little about the basic defects in noninsulin-dependent diabetes, or Type II diabetes. Type II diabetes may result when the body's cells are unable to use the insulin that is present. We do know that Type II diabetes is aggravated by obesity and ameliorated by diet and exercise. In the Fall of 1986, the NIDDK will host a Consensus Development Conference on diet and exercise in the treatment of noninsulin-dependent diabetes. This conference may focus directions for future investigation. Meanwhile, basic research into the nature of insulin action may provide the clues we need to decipher the defects underlying Type II diabetes. When these defects are better characterized, we will be able to pursue specific preventive strategies.

Mr. Stokes. Is the incidence of diabetes in Blacks increasing or decreasing? Why?

Dr. Renault. The percent of Black Americans who have diabetes is most definitely increasing for the type of diabetes that occurs in adults, which we call Type II or noninsulin-dependent diabetes (NIDDM). In 1970, about 3.4 percent of Black adults in the U.S. had been diagnosed as having NIDDM; in 1981, the most recent year for which we have national data from surveys of our sister agency, the National Center for Health Statistics, about 5.4 percent of Black adults, or about 850,000 people, had been diagnosed as having NIDDM. Based on a study conducted by NIADDK and NCHS in 1976-80, we believe there are an additional 600,000 Black adults who have NIDDM but who are currently undiagnosed.

For the type of diabetes that tends to occur in children and young adults (which we call Type I or insulin-dependent diabetes), however, the rates appear to have been essentially constant for at least the past 20 years.

We believe the increase in numbers of adult Blacks with diabetes is likely due to an increasing lifespan for Black diabetics, for we have seen a marked decline in their death rate. The death rate attributed to diabetes in Blacks peaked in about 1972; in the decade since that year, the rate has declined as much as 30 percent. Many factors may be contributing to this remarkable and welcome phenomenon, but our studies do not yet permit us to interpret the reasons for this decline. Some factors that we surmise may be related include better medical care of the acute complications of diabetes; more attention to control of blood glucose; decreases in hypertension which particularly complicates diabetic kidney disease; and decreases in the cardiovascular diseases that are so prominent in diabetic Blacks, especially ischemic heart disease and stroke.

Mr. Stokes. To what extent will Blacks be included among the 1400 patients who will participate in Phase III of the Diabetes Control and Complications Trial?

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Dr. Renault. Of the 278 subjects recruited for the DCCT feasibility study, 2.5 percent were Black Americans. While this proportion is somewhat smaller than would be expected based on the prevalence of Type I diabetes in the Black population, we believe it can be attributed to two factors that were specific to the feasibility study but will not necessarily be operative in the full-scale trial.

The first of these is related to the geographic distribution of the 21 clinical centers that participated in the feasibility study. A significant number of these centers were located in areas with small populations of Blacks. We are currently recruiting additional clinics in major urban centers for participation in the full-scale trial. We anticipate that some of these new centers will be located in areas with higher proportions of Blacks and other minorities.

The second factor to note is that the number of subjects recruited at each clinical center during the feasibility study was small. The average number of subjects per clinic recruited in the feasibility study was 13. Therefore, due to the small number of subjects at each clinic, the demographic characteristics of these DCCT subjects may not be reflective of the demographic characteristics of the clinic's location. In Phase III, 55 - 60 subjects will be recruited by each clinic, and it is anticipated that this larger number of subjects will be more representative of the composition of the population within the catchment area of each clinic.

DIABETES CONTROL AND COMPLICATIONS TRIAL

Mr. Stokes. What do you hope to learn from this clinical trial?

Dr. Renault. The DCCT will address two of the most important clinical questions in diabetes today, namely:

(a) Whether the derangements of glycemic control which characterize the diabetic state are associated with development of the life-threatening and disabling complications of this disease; and

(b) Whether it is possible to intervene in this process so as to prevent these complications.

The DCCT will determine the most effective form of therapy for persons with insulin-dependent diabetes, and these results will direct the future course of treatment of all persons with insulin-dependent diabetes. It is hoped that we will learn from this trial how to prevent the dreaded complications of diabetes, thereby improving the quality of life for all Americans afflicted with this illness.

CYSTIC FIBROSIS

Mr. Stokes. What research activities are being conducted at the Cystic Fibrosis Core Research Center?

Dr. Renault. An excellent program for comprehensive care of patients with cystic fibrosis, which has attracted nearly 500 patients, makes the Cystic Fibrosis Research Center at Case Western Reserve University the largest such center in the country. This patient resource provides the opportunity for clinical investigation into the course of the illness, its complications, and therapeutic interventions. Clinical studies focus on glucose intolerance in cystic fibrosis patients, pulmonary and kidney pathology, biochemical mechanisms of lung damage, airway responsiveness and the regulation of airway size, and host defenses against pulmonary pathogens.

Because there is no adequate animal model for cystic fibrosis, tissues, secretions, and other specimens from these patients are vital for laboratory research as well. Cell samples maintained at the Center from an important kindred of Amish patients with cystic fibrosis are an important resource for research into the genetics of cystic fibrosis. Studies are planned to exploit the genetic probes and markers for cystic fibrosis which have recently been identified at several centers.

A major focus of research at the Center involves the epithelial cell, which is the major cell type expressing the cystic fibrosis phenotype. Some specific studies in progress include the development of methods for growth of these cells in culture and the comparison of electrical properties, synthesis and secretion of macromolecules, and response to injury in normal and cystic fibrosis epithelial cells. Epithelial cells from sweat ducts and coils, the trachea, and the kidney are being studied to investigate tissue-specific abnormalities in cystic fibrosis.

Other studies focus on ion transport mechanisms and intracellular mediators such as calcium, cyclic-AMP, and phosphatidyl inositol. These experiments are aimed at elucidating the basic defect which causes cystic fibrosis, with the ultimate goal of development of treatment strategies to compensate for the basic defect and thus to alleviate the symptoms of cystic fibrosis.

Research is also aimed at increasing our understanding of the synthesis, processing, structure, and transport of mucins and other secreted macromolecules which are responsible for the thick secretions which obstruct pulmonary and gastrointestinal ducts in people with cystic fibrosis. The abnormal mucous causes respiratory failure and malabsorption which ultimately shorten the life span of cystic fibrosis patients.

Mr. Stokes. What are the budget allocations for this Center in 1985, 1986, and 1987?

Dr. Renault. The NIADDK Cystic Fibrosis Center received $665,982 in 1985, a reduction of about four percent from the recommended amount. The NIDDK Cystic Fibrosis Center budget recommended by the Intial Review Group was $795,964 for the year beginning in April 1986. Institute-wide reductions in recommended funding levels will reduce the level of support to $695,000. The recommended funding level for 1987 is $703,702, but the actual level of funding has not yet been determined.

LITHOTRIPTOR

Mr. Stokes. I have heard about the new lithotriptor machine that crushes kidney stones using shock waves, thereby eliminating the need for surgery for kidney stone patients. How widely used is this new technology?

Dr. Renault. The incidence of open kidney surgery for stones in locales having access to the lithotriptor has dropped to nearly zero, and percutaneous approaches have decreased by 80 percent. As of six weeks ago, there were 62 machines in the U.S. with new ones being installed at a rate of 6 per month. This same assessment which was completed for the manufacturing company estimates that within the next year there will be 120 machines in the U.S. This number should be sufficient to meet the anticipated need.

Mr. Stokes. What role, if any, did NIH play in the development of the lithotriptor?

Dr. Renault. The NIH did not directly support the development of the technology or instrumentation for the lithotriptor. The NIH did support research on the composition of stones providing the data which determined the feasibility of the technique. Thus, we believe that this event demonstrates the effectiveness of the NIH providing support for fundamental research which can then be utilized by private industry in the development of the appropriate instrumentation. The NIH also continues to support research on the prevention of recurrent stones.

MINORITY PROGRAMS

Mr. Stokes. Dr. Renault, your Institute studies a great many diseases that disproportionately affect Blacks. Yet, in 1984, only $317 thousand was awarded to historically Black colleges. Why is that?

Dr. Renault. In 1984, the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases made four awards for $317 thousand to investigators at historically Black colleges. Applicants from these institutions compete for available funds on the basis of scientific merit of the proposed projects.

Mr. Stokes. Last year, you indicated that no goals for making awards to historically Black colleges were established by your institute. Yet, other institutes at NIH set such goals. Why should your Institute be any different?

Dr. Renault. As I mentioned earlier, in this Institute applications from investigators at historically Black colleges compete for available funds on the basis of the scientific merit of the proposed projects. The NIDDK has made every effort to encourage investigators from these institutions to apply for research support, and furthermore have offered to supply them with guidance in preparing their applications in the hopes of strengthening their chances for submitting successful applications.

Mr. Stokes. Specifically, please indicate what your Institute is doing to expand research and research training opportunities for minority scientists, excluding the minority biomedical research support program and the MARC program? Also, indicate the dollar allocations associated with any such initiatives.

Dr. Renault. In order to increase the participation of underrepresented minority investigators, the NIDDK plans to establish the Minority Investigator Research Enhancement Award (MIREA). The MIREA will support minority investigators who have completed their training but have not served as principal investigators on NIH regular research grants. The MIREA researchers will collaborate with investigators currently funded by a NIDDK research grant or center program. The Institute hopes this association will provide MIREA investigators with experience and the elements of grantsmanship that will enable them to be competitive within the NIH peer review system.

An announcement about the MIREA award has recently been published in the NIH Guide to Grants and Contracts, and all eligible applicants will be funded up to a program total of $350,000 in FY 1987.

Mr. Stokes. What is your Institute doing to increase the number of minorities supported through institutional training grants that go to nonminority institutions?

Dr. Renault. No specific goals have been set for 1986 or 1987 for increasing the number of minorities supported through institutional training grants that go to nonminority institutions.

We are currently preparing new guidelines for investigators who are preparing an institutional training grant application. The applicant will be required to include a description of specific plans for recruitment of minorities and of the past record of the institution in the selection of minorities. Subsequent review of the application at NIH will include an assessment of the institution's activities regarding minority training.

Mr. Stokes. Do you establish goals for your senior administrators for addressing minority program and personnel issues? If not, why not?

Dr. Renault. The Institute has made equal employment opportunity and affirmative action goals an essential element of the performance appraisal of each of its senior administrators.

Programatically, the Institute encourages senior administrators to support the Minority Access to Research Careers program and the Minority Biomedical Research Support program. Our scientists also have had a rather consistent record of visiting minority institutions, of remaining there for a week, teaching and advising staff scientists. In addition, we have always had a very good representation in our summer program, that is, with students from minority institutions. We have a large investment in sickle cell anemia and in terms of minority populations, we have a large investment in research on diabetes among the Pima Indian.

Mr. Stokes. How do you hold your senior officers accountable for meeting those goals?

Dr. Renault. The work performance of every senior administrator in the Institute is reviewed annually to evaluate whether the employee's performance has met the goals set forth at the beginning of the appraisal period. This evaluation becomes part of the official personnel record of each senior administrator.

Mr. Stokes. For the record, please supply the following information for SES, senior level administrative, and senior level professional positions in your Institute: the current number of all such positions and the current number of these positions occupied by Blacks.

Dr. Renault. Of the 104 positions in these categories, nine are occupied by Blacks. Despite significant efforts, we have had little success in recruiting Black M.D.'s and Ph.D.'s at any level who could advance to most of these types of positions.

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Mr. Early. How was the amount of the rescission, $7.980 million, for NIDDKD arrived at?

Dr. Renault. While the total amount of the FY 1986 rescission for research project grants was mandated by OMB, the Office of the Director, NIH had the responsibility of allocating the total reduction and assigning specific rescission amounts to the Institutes. The amount of each Institute's rescission was determined in two steps. First, a simple proration of the total rescission was first computed against each Institute's funding for research project grants and then these amounts were adjusted further to reflect NIH research priorities.

Mr. Early. Why is a $7.980 million rescission being proposed on top of a reduction of $24.482 million due to sequestration?

Dr. Renault. The FY 1987 policy of stabilizing research project grant funding at 18,000 grants and the desirability of providing a smooth transition from FY 1985 through FY 1987 have necessitated this proposal to rescind $7.980 million in FY 1986. In order for NIH to achieve the 18,000 grants target without seriously reducing the number of competing research project grants in FY 1987, the number of competing awards in FY 1986 had to be reduced and the funding associated with it rescinded.

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IMPACT OF BUDGET REDUCTIONS

Mr. Early. What would the impact of sequestration AND rescission be?

Dr. Renault. Under the sequestration, each budget mechanism is reduced by 4.3 percent. In research grants and research centers the numbers of awards will be maintained but negotiated reductions in each award will be increased an average of 4.3 percent. In the other mechanisms, such reductions are not possible and 7 research career awards, 37 National Research Service Award trainees, and one contract will be cut. Under the proposed rescission, which applies only to research grants, 73 fewer new and competing awards would be made, in order to fund more fully the 564 new and competing awards estimated to be made in 1986.

Mr. Early. Under the FY 86 enacted level, NIDDK would be able to fund 637 new and competing research grants. Under the Administration's revised FY 86 proposal, NIDDK would fund only 564 or 73 fewer? Doctor, would you tell us briefly what areas of research would be affected by this reduction?

Dr. Renault. Since our funding decisions are primarily determined by the priority scores and percentiles given by the scientific peer review groups, this reduction will probably be distributed proportionately among our various programs and disease categories. We will however give special attention to smaller program areas to ensure that they are not disproportionately effected or the viability of the programs impaired.

Mr. Early. What percentage of approved grants would be funded under the FY 86 revised and the FY 87 budget requests? How does this compare to your original FY 86 estimate? How does it compare to FY 85?

Dr. Renault. Our award rates are projected at 31 percent under the 1986 Revised Estimate and 29.9 percent in the 1987 Request. These compare to rates of 35 percent under the 1986 Appropriation and 37 percent in 1985.

Mr. Early. According to the budget justification, there will be downward negotiations of 13.5 percent and 14.4 percent in competing and non-competing grants, respectively. Will each grant be reduced by these amounts? What impact will reductions of this size have on the Institute's research activities?

Dr. Renault. These are the average reductions which we will need to achieve, but each grant will be looked at individually and some will be cut more and some will be cut less. It is our judgment that cuts above five or six percent will have a significant impact on the quality and depth of the proposed scientific investigations. In addition to reductions in supplies and material, at higher reduction levels, support personnel will probably have to be cut.

Mr. Early. In your professional judgment, Doctor, do you have any serious concerns about the size of the downward negotiations the project grants are being forced to take under this budget request?

Dr. Renault. Yes, we do. As I have just stated, we believe that at these levels of reductions, support staff will need to be cut and the time necessary to develop meaningful findings will be elongated.

RESEARCH CENTER GRANT CUTS

Mr. Early. The budget indicates that direct costs for research centers will be reduced by 13 percent in FY 86 and then 20 percent in FY 87. Are reductions of this size something we need to be concerned about?

Dr. Renault. We believe less research will be accomplished than had been planned. In 1984 and 1985, the reductions were only six percent and four percent respectively.

Mr. Early. What effect will these cuts have on the research programs at these centers?

Dr. Renault. We expect to be able to maintain the basic core functions of each center but some individual projects and feasibility studies will have to be eliminated.

Mr. Early. How will the reduction in the size and scope of the centers program affect NIDDK's program plans--both immediate and long range?

Dr. Renault. All plans for a new kidney centers program or an expanded digestive diseases program have been indefinitely postponed. We will focus on maintaining the basic core functions of our current centers.

RESEARCH CENTER GRANT RENEWALS

Mr. Early. I understand that 31 research centers are to be supported in FY 86 and in FY 87. How many centers are up for renewal in FY 86?

Dr. Renault. Only five centers are up for renewal, all in the diabetes program. In addition, we have one recently approved, very good new application so we have six applications competing for five slots.

Mr. Early. For the record provide the names and locations of these centers.

Dr. Renault. Those up for renewal include one Diabetes and Endocrinology Research Center located at University of Pennsylvania in Philadelphia (Dr. Matschinsky, principle investigator); one Obesity Center at St. Luke's Hospital in New York City (Dr. Van Itallie, principle investigator); one Cystic Fibrosis Center at Case Western Reserve University in Cleveland, Ohio (Dr. Davis, principle investigator); and two Diabetes Research and Training

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Centers at Indiana University in Indianapolis (Dr. Clark, principle investigator); and at the University of Virginia in Charlottesville (Dr. Larner, principle investigator). The new application is for a Diabetes Research and Training Center at the Joslin Diabetes Research Center in Boston (Dr. Kahn, principle investigator).

Mr. Early. Also, provide a comprehensive list of all the centers supported by NIDDK.

Dr. Renault. The list of all the centers supported in 1985 follows:

Diabetes-Endocrinology Research Centers		FY 1985 Funding
University of Washington Seattle, WA	Dr. Porte	$906,000
University of Pennsylvania Philadelphia, PA	Dr. Matschinsky	$794,000
Iowa University Iowa City, IO	Dr. Ginsberg	$747,000
Baylor School of Medicine Waco, TX	Dr. Field	$527,000
University of Massachusetts Amherst, MA	Dr. Chick	$630,000
Diabetes Research and Training Centers		
Yeshiva University New York City, NY	Dr. Fleischer	$1,425,000
Indiana University Indianapolis, IN	Dr. Clark	$946,000
University of Michigan Ann Arbor, MI	Dr. Fajans	$1,987,000
Washington University Saint Louis, MO	Dr. Daughaday	$1,625,000
Vanderbilt University Nashville, TN	Dr. Crofford	$340,000
University of Chicago Chicago, IL	Dr. Tager	$2,044,000
University of Virginia Charlottesville, VA	Dr. Larner	$1,258,000
Obesity Center		
St. Luke's Hospital New York, NY	Dr. Van Itallie	$735,000

Cystic Fibrosis Center

Case Western Reserve Univ. Cleveland, OH	Dr. Davis	$808,000

Digestive Disease Centers

University of California San Francisco, CA	Dr. Ochner	$745,000
Yeshiva University New York City, NY	Dr. Shafritz	$967,000
Beth Israel Hospital Boston, MA	Dr. Silen	$698,000
University of Colorado Boulder, CO	Dr. Simon	$413,000
New England Medical Center Boston, MA	Dr. Donowitz	$387,000
University of Minnesota Minneapolis, MN	Dr. Bloomer	$632,000
University of Michigan Ann Arbor, MI	Dr. Yamada	$145,000
University of Iowa Iowa City, IO	Dr. Christensen	$628,000
University of North Carolina Chapel Hill, NC	Dr. Powell	$667,000
Mayo Foundation Rochester, MN	Dr. Phillips	$273,000
Yale University New Haven, CT	Dr. Boyer	$705,000
Harbor General - UCLA Medical Center Los Angeles, CA	Dr. Snape	$924,000

Clinical Nutrition Research Units

University of Wisconsin Madison, WI	Dr. Harper	$216,000
University of Chicago Chicago, IL	Dr. Rosenberg	$626,000

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University of Washington Seattle, WA	Dr. Bierman	$562,000
Vanderbilt University Nashville, TN	Dr. Greene	$796,000
University of Colorado Davis, CA	Dr. Halstead	$477,000

Mr. Early. How many centers will be up for renewal in FY 87?

Dr. Renault. There will be five centers up for renewal in 1987, four in diabetes and one in digestive diseases.

Mr. Early. Provide the names and locations of these for the record.

Dr. Renault. The list of those up for renewal in 1987 follows:

Diabetes-Endocrinology
Research Centers

University of Washington Seattle, WA	Dr. Porte
Iowa University Iowa City, IO	Dr. Ginsberg
Baylor School of Medicine Waco, TX	Dr. Field

Diabetes Research and
Training Center

University of Chicago Chicago, IL	Dr. Tager

Digestive Diseases Center

Yeshiva University New York City, NY	Dr. Shafritz

CLINICAL TRIALS

Mr. Early. How many new clinical trials will be started during FY 86?

Dr. Renault. We have initiated or plan to initiate five major clinical trials in FY 1986.

Mr. Early. Provide a list of the clinical trials which will be underway in FY 86, and indicate which ones are new.

Dr. Renault. We will have over 100 clinical studies in 1986. A list of the major ones follows:

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Major New Clinical Studies

Diabetes Control and Complications Trial (beginning of full scale trial)

Dietary Modification and the Progression of Renal Disease

Testing of the Safety and Efficacy of Treating Lactic Acidosis with Dichloroacetate

Effects of Diet on Progression of Renal Disease in the Pima Indians

Effectiveness of Diet Therapy for Prevention of Progression of Renal Disease in Children

Continuing Major Clinical Studies

Pulmonary Benefit of Cystic Fibrosis Neonatal Screening

Study of Plasmapheresis in Severe Lupus Nephritis

Formulation of Rational Therapy for Nephrolithrosis

Gastrointestinal Hormones: Studies of Gastric Emptying and Secretion

Studies of the Natural History and Treatment of Chronic Type B Hepatitis

Growth Failure in Children with Renal Disease

Mr. Early. Will you have to curtail any ongoing clinical trials with your FY 86 revised budget request? If so, which ones?

Dr. Renault. Most of our current clinical trials are carried out through research grants and except for the Diabetes Control and Complications Trial and the trial on Modification of Diet in Renal Diseases, which will be partially protected to maintain the integrity of these studies, our other clinical trials will be reduced about ten percent.

Mr. Early. Doctor, will you have to curtail any ongoing clinical trials with your FY 87 budget request? If so, which ones?

Dr. Renault. The situation in 1987 will be about the same as I just described for 1986, except that the reductions would be between twelve and fifteen percent.

Mr. Early. Will you be able to start any new clinical trials in FY 87?

Dr. Renault. No, sir. We will not be initiating any major new clinical trials under the current budget proposal.

Mr. Early. Are there any high priority clinical trials which are ready but cannot be initiated because of lack of funds in the FY 87 request? If so, please provide a list of these, along

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with a brief description and the associated costs, including first year costs.

Dr. Renault. The following are the high priority major clinical trials which would be appropriate to initiate in 1987:

Additional NIDDK Clinical Trials Which Could be Initiated in 1987

	Estimated Costs ($ in thousands)	
	FY 1987	Total
o Treatment of Short Stature with Human Growth Hormone. A clinical trial has been proposed to study the safety and efficacy of biosynthetic growth hormone with and without oxandrolone in treating children with short stature not due to growth hormone deficiency.	$420	$1,400
o Nonsurgical (Balloons) Reduction of Stomach Capacity in the Treatment of Morbid Obesity. Balloon therapy for reducing stomach capacity may be an effective method for treating morbid obesity which could avoid surgery and its inherent risks. The Digestive Diseases and Nutrition Subcouncil of the National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council has recommended that a request for applications be issued for a clinical trial to test the safety and efficacy of balloon therapy for morbid obesity.	$212	$464
o Postoperative Decompression Feeding Trial. A multicenter clinical trial of early postoperative bowel decompression and feeding has been proposed. This would test a variety of interventions, with the goal of reducing the duration of postoperative hospital stays, in approximately 600 surgical patients.	$4,785	$25,500
o Kidney Transplantation in Children with ESRD. A clinical trial to determine the	$250	$1,000

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optimal protocol for kidney transplantation for children with end-stage renal disease has been proposed.		
o Expanded Nephrologic Component of the DCCT. If additional funds were made available, consideration would be given to funding an expanded nephrologic component of the Diabetes Control and Complications Trial (DCCT) which would test the benefit of early intensive treatment of insulin-dependent diabetes mellitus on the development and progression of diabetic nephropathy. This complication of diabetes accounts for approximately one-fourth of the new cases of end-stage renal disease in the United States each year.	$480	$6,650
o Controlled Clinical Trial of Hematin Therapy for Acute Porphyric Attacks. A multicenter, controlled clinical trial of hematin, an orphan drug, would attempt to determine the optimum dosage and timing of administration to prevent acute porphyric attacks. Approximately 150 patients would be randomized to hematin therapy or glucose infusion (the current therapy). Adverse effects of hematin on hemostasis would be monitored.	$450	$2,500

SMALL BUSINESS INNOVATIVE RESEARCH

Mr. Early. Doctor, briefly would you tell us how your Institute is using the Small Business Innovation Research Program? Then for the record provide a bit more detail.

Dr. Renault. The Institute is using the Small Business Innovation Research (SBIR) Program to apply advanced technologic resources and original thinking of small businesses to development of needed new diagnostic techniques, therapeutic agents and devices, computerized data bases, and tools for biomedical research and patient education. Research areas involved include diabetes, digestive diseases, nutrition, anemia, and kidney and urologic diseases.

In the area of diabetes, SBIR studies seek to improve diabetes treatment and self-care. One study aims to apply recombinant

DNA techniques to facilitate the development of a definitive test for islet cell antibodies. Other SBIR projects are designed to develop improved blood glucose sensors and a more sensitive assay for monitoring diabetic control. The goal of three additional studies is to apply computer technology to enhancing diabetes selfcare.

A group of SBIR awards in nutrition research focuses on novel means of nutrition assessment. One such NIDDK project is developing a comprehensive research data base on vitamins and minerals for use in assessing nutrition intake. The SBIR program is supporting development of interactive software for self reported diet assessment. The Institute is funding an effort to develop a tool which would increase the reliability of measurement of body fat, an important factor in the diagnosis and treatment of many serious health disorders.

The SBIR grants in kidney and urologic diseases range from a study to develop a new pharmacologic means of protecting the kidney from ischemia to a study on laser fragmentation of urinary calculi. Another project focuses on inhibition of urinary tract infections associated with the use of urinary drainage catheters. These studies hold the promise of reducing significant clinical problems often responsible for prolonged hospitalization and increased morbidity and mortality.

Mr. Early. Would you give us a few examples of how the Institute utilizes its Research and Development Contract mechanism?

Dr. Renault. Major contract programs of this Institute include a hormone distribution program (four contracts), the coordinating center for the Diabetes Control and Complications Trial, two tissue banks for the diabetes and cystic fibrosis programs, a Liver Transpslant Registry, a contract to breed and distribute BB Wistar rats (a diabetes animal model), two information clearinghouses for diabetes and digestive diseases, several contracts to develop and test chelating agents to treat Cooley's Anemia and a new major clinical trial to assess the effects of diet on the progression of diabetic nephropathy in the Pima Indians.

RESEARCH CONTRACTS

Mr. Early. Under your FY 87 request, you will be supporting only 30 R&D contracts, as compared to the FY 86 post-sequestration level of 32. What impact will it have on your research initiatives?

Dr. Renault. In 1987, we will have no contract initiatives.

Mr. Early. Is it correct that in FY 85, 24 contracts were supported? What effect does this "unstableness" have on your programs?

Dr. Renault. As you noted, our contract program has expanded since 1985, providing us stability over the long run. As a result of budget cutbacks in 1986, we will need to cut back our distribution programs for hormones and the BB Wistar rat (diabetes animal model).

USE OF ADDITIONAL FUNDS

Mr. Early. If an increase over the FY 87 request is provided, how would you use these additional funds?

Dr. Renault. Our priorities would be to provide a significant increase for Research Career Awards to revitalize that program; to restore recent reductions in both manpower and funding for intramural research, and finally to more fully fund regular research and centers grants.

RESEARCH INITIATIVES

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed by lack of funds in the FY 87 budget?

Dr. Renault. We always have plans and initiatives beyond our current budgetary resources.

Mr. Early. Please provide for the record a list of these, along with a brief description and the funding requirements associated with each.

Dr. Renault. Our list of potential new initiatives which will not be supported under the current budget proposal follows:

New Initiatives and Opportunities

Clinical Trials	Estimated Requirements
Expanded Nephrologic Component of the DCCT. If additional funds were made available, consideration would be given to funding an expanded nephrologic component of the Diabetes Control and Complications Trial (DCCT) which would test the benefit of early intensive treatment of insulin-dependent nephropathy. This complication of diabetes accounts for approximately one-fourth of the new cases of end-stage renal disease in the United States each year.	$480,000
Nonsurgical (Balloons) Reduction of Stomach Capacity in the Treatment of Morbid Obesity.	$212,000

Balloon therapy for reducing stomach capacity may be an effective method for treating morbid obesity which could avoid surgery and its inherent risks. The Digestive Diseases and Nutrition Subcouncil of the National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council has recommended that a request for applications be issued for a clinical trial to test the safety and efficacy of balloon therapy for morbid obesity.

Postoperative Decompression Feeding Trial. $4,800,000

A multicenter clinical trial of early postoperative bowel decompression and feeding has been proposed which would test a variety of interventions with the goal of reducing the duration of postoperative hospital stays in approximately 600 surgical patients.

Kidney Transplantation in Children with ESRD. $250,000

A clinical trial to determine the optimal protocol for kidney transplantation for children with end-stage renal disease has been proposed.

Controlled Clinical Trial of Hematin Therapy for Acute Porphyric Attacks. $450,000

A multicenter, controlled clinical trial of hematin, an orphan drug, would attempt to determine the optimum dosage and timing of administration to prevent acute porphyric attacks. Approximately 150 patients would be randomized to hematin therapy or glucose infusion (the current therapy). Adverse effects of hematin on hemostasis would be monitored.

Treatment of Short Stature with Human Growth Hormone. $420,00

A clinical trial has been proposed to study the safety and efficacy of biosynthetic growth hormone with and without oxandrolone in treating children with short stature not due to growth hormone deficiency.

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Division of Diabetes, Endocrinology and Metabolic Diseases

Interdisciplinary Studies in Diabetes and Endocrinology. $1,000,000

This new initiative to expand support for Diabetes/Endocrinology Centers, including congressionally-mandated Diabetes Research and Training Centers, will be postponed. Award of 1 highly meritorious application which was initially postponed during FY 1986 will be postponed indefinitely.

Research on Endocrine Transplantation. $1,800,000

This major new initiative to capitalize on recent research advances through expansion of support for research and research resources related to transplantation of endocrine tissues, including pancreatic islet cell transplants to cure juvenile diabetes, will be deferred.

Tissue Resources for Biomedical Research. $500,000

This new initiative to develop a centralized mechanism for the procurement and distribution of human tissues for research and transplantation, will be postponed.

Treatment of Diabetes in America. $20,000

The new initiative to assess current attitudes and practices of physicians that relate to the treatment of people with diabetes will be deferred.

Assessment of Diabetes Mortality. $25,000

This new initiative to analyze the rates and causes of death among diabetics in the 14 center WHO Multinational Study of Diabetes Mortality will be postponed.

Data System. $1,000,000

Recent Congressional action (Pubic Law 99-158) mandated the establishment of a National Diabetes Data System for the collection, storage, analysis, retrieval and dissemination of data derived from patient populations with diabetes, although no funds have been requested for this purpose.

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Division of Digestive Diseases and Nutrition

Gallstone Prevention. $1,000,000

There is a significant national need for scientific studies on gallstone prevention, including a clinical trial on gallstone prevention through dietary intervention.

Treatment of Anorectal Crohn's Disease. $400,000

The anorectal manifestations of Crohn's disease are refractory to treatment, extremely debilitating and very costly. Metronidizole is being used in treatment, but has never been studied for efficacy in the treatment of Crohn's disease, even though it is known to present risks (neurological and carcinogenic) to the patient.

Treatment of Diarrheal Diseases. $750,000

Diarrhea remains a serious problem in the United States, and a major cause of morbidity and mortality in third-world countries. Patient treatment opportunities exist to expand effective treatment of diarrhea beyond anti-microbial approaches and the use of opiate derivatives. New approaches would take advantage of messenger chemicals and receptors that exist naturally in the body.

Nutritional Support of Patients. $740,000

Studies are planned on alternative lipid sources for patients on total parenteral nutrition, in particular to address metabolic and physiological functions of currently used fat emulsions and to seek possible better sources of fat: physical and structural mixtures of medium and long chain triglycerides

Research Training in the Epidemiology of Digestive and Nutritional Diseases and Disorders. $500,000

Skilled investigators in these areas are few, and thus a much needed knowledge base in epidemiology is inadequate. Once achieved, such knowledge will provide insight for needed research directions and

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for more effective treatment of these diseases and disorders.

Clinical Nutrition Research Center. $800,000

The complex, interdisciplinary nature of clinical nutrition research indicates the need for centers which foster such nutrition research excellence; however, only 8 such centers exist in the United States. The availability of a CNRU provides a nucleus of investigators which can foster a multidisciplinary approach to nutrition-related disorders.

Data System. $1,000,000

Recent Congressional action (Public Law 99-158) mandated the establishment of a National Digestive Diseases Data System for the collection, storage, analysis, retrieval and dissemination of data derived from patient populations with diabetes, although no funds have been requested for this purpose.

Division of Kidney, Urologic, and Hematologic Diseases

Specialized Centers of Research. $5,000,000

Centers in Kidney and Urologic Disorders can be realistically expected to lead to advances which will lead to a 25 percent decrease in the incidence of end-stage renal disease and benign prostatic hyperplasia in the next decade. The centers would serve the purpose of bringing new investigators and techniques into the field and focusing on these major health problems.

Epidemiological Surveillence of End-Stage Renal Disease (ESRD) Treatment in the U.S. $350,000

The morbidity of ESRD treatments (dialysis and transplantation) are substantial, but not well-documented. Considerable progress needs to be made in reducing the incidence of their short-term and long-range consequences which lead to shortened life span, decreased ability to resume a normal work schedule, and increased morbidity. This initiative would provide the data to evaluate the differing methods of dialysis

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(including dialyzer reuse) and kidney transplantation.

Improve Availability of Blood Cell Precursors and Growth Factors for Clinical and Research Use in Blood Disease. $650,000

The treatment of anemias and general bone marrow failure is still a major investigative area at both the clinical and basic levels. The availability of the above would greatly facilitate these studies in the most cost-effective manner.

Isolation and Characterization of the Androgen Receptor in Prostatic Tissue. $450,000

Benign prostatic hyperplasia is the most common morbid condition of males over the age of 50. There is good evidence that androgens play a large role in this disease but few data are available on their direct effects on the prostate. A contract effort to isolate and characterize the androgen receptor would provide the tools to directly study this important disease.

Study of In Vitro Techniques and Conditions for the Culture of Kidney Cells Expressing a Differentiated Phenotype. $450,000

The DKUHD funds basic research which depends on cells in culture as one of its major thrusts in the approach to kidney, urologic and hematologic diseases. Therefore, a central focus on improving in vitro techniques is essential.

Molecular Mechanisms in Renal Transplantation $3,000,000

Renal transplantation is the end-stage renal disease treatment favored by patients and physicians, is the most cost-effective, and results in the best patient rehabilitation. Rejection of the transplanted kidney and waste of kidneys due to failure to find the appropriate recipient are currently at unacceptably high levels. Thus, basic research is needed to address the issues of the mechanism of immunologic reaction of and to the kidney transplant.

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National Advisory Board, Clearinghouse, and Data System.	$1,600,000

Recent Congressional action (Public Law 99-158) mandated the establishment of a National Kidney and Urologic Diseases Advisory Board, but the current budget request includes no provision for establishing the Board. This legislation also authorized the establishment of a National Kidney and Urologic Diseases Information Clearinghouse and a National Kidney and Urologic Diseases Data System, for which no funds have been requested in 1987.

Mr. Early. Doctor, will any significant research initiative currently underway be halted or seriously delayed due to FY 87 funding levels?

Dr. Renault. Three small, recently initiated programs will have to be abandoned. These include a program focused on minority health problems and physician education, a grant program to upgrade and replace moderately-priced high priority scientific instruments, and a Small Grants program focused on orphan diseases.

Mr. Early. To what extent will there be major reductions in the scope of ongoing or new initiatives because of the FY 87 funding levels?

Dr. Renault. Most of our current initiatives are carried out through research grants and except for the Diabetes Control and Complications Trial and the trial on Modification of Diet in Renal Disease which will be partially protected to maintain the integrity of these studies, our other initiatives will be reduced by twelve to fifteen percent.

Mr. Early. For the record, provide a list of these along with a brief description and the amount associated with each initiative.

Dr. Renault. A list of our ongoing initiatives which would be most heavily impacted follows:

ONGOING INITIATIVES

	Estimated Needs
Intramural Research.	$6,300,000

Intramural research activities, particularly clinical studies in diabetes, digestive diseases, and kidney diseases will be significantly hampered. The scope of basic research in areas such as cystic fibrosis and nutrition will also be reduced. Adoption of new research techniques will be slowed by lack of sufficient funds to upgrade research equipment. The interchange of fresh theories and research strategies will be compromised by the reduction of twenty-five promising young international researchers invited to occupy temporary research positions in our laboratories and clinical branches.

Study of Diabetic Renal Disease in the Pima Indian Population. $250,000

This comprehensive study has been initiated in 1986. This will be a several year multifaceted study of the epidemiology, natural history and pathogenesis of renal disease, as well as a clinical trial to assess the effects of intervention strategies on the progression of diabetic renal disease. The Pima Indians are a unique population whose diabetic profile has been under long-term study. Planned activities in 1987 and beyond will be seriously attenuated if funds are greatly restricted.

Research Career Awards. $300,000

The NIDDK has a substantial shortfall in the research career award category so that no new career awards can be made in FY 1986 and FY 1987. In addition, current institutional Physician Scientist Awards will be capped at five slots rather than the ten originally planned. This is particularly devastating because the NIDDK is the primary disease-oriented institute with a substantial commitment to basic research and the training of MD basic researchers.

Minority Health Initiative. $200,000

Plans for this initative have recently been completed, to include an epidemiologic study of the incidence of Type II diabetes and renal disease in Blacks and other minority populations. Also planned are physician education activities, to emphasize the seriousness of these diseases in minority populations. Proposed 1987 budget levels would preclude this effort.

Treatment of Growth Disorders in Children. $1,100,000

The National Hormone and Pituitary Program supports the centralized collection of pituitary glands and the extraction/distribution of rare hormones and antisera to foster research related to growth disorders and other endocrine diseases. It is proposed to reduce contract support for this ongoing program by 65 percent

Prevention of Juvenile Diabetes. $500,000

A unique animal models program supports the centralized production, characterization, and distribution of rare BB-Wistar rats to foster research related to the cure and prevention of juvenile-onset diabetes. It is proposed to reduce contract support for this ongoing program by 80 percent.

High Priority Scientific Instruments. $1,500,000

This program, which is proposed for termination, supports the purchase of moderately-priced high priority scientific instruments which will be shared by 2 or more established investigators for studies including diabetes, endocrinology, and metabolic diseases.

Small Grants on Orphan Diseases. $500,000

This program, which is proposed for termination, is designed to support innovative and/or high risk pilot projects related to inherited metabolic diseases, including cystic fibrosis.

Patient and Professional Education Related to Diabetes. $150,000

It is proposed that contract support for the congressionally-mandated National Diabetes Clearinghouse be reduced by 30 percent.

DIABETES RESEARCH AND TRAINING CENTERS

Mr. Early. Doctor, how will the Multipurpose Diabetes Research & Training Centers fare under the FY 87 budget request?

Dr. Renault. We estimate that each of the Multipurpose Diabetes Research and Training Centers will have to be reduced by about twenty percent.

DIABETES RESEARCH

Mr. Early. What are the latest advances in diabetes research? Would you bring us up to date on what is being done in this area?

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Dr. Renault. The most recent advances in diabetes research are in an understanding of the role of immune mechanisms in Type I diabetes, in developing strategies for pancreas/islet cell transplantation, in clarifying the structure of the genes for insulin and the insulin receptor, and in clarifying the mechanisms of insulin action.

Rapid progress is being made in understanding the immune mechanisms in insulin-dependent (Type I) diabetes. Immune mechanisms are responsible for the destruction of the insulin-producing beta cells leading to the onset of Type I diabetes. An understanding of these immune mechanisms may lead to methods to prevent this kind of diabetes. Furthermore, there are also efforts underway to use transplantation of either islet cells or portions of pancreas to cure individuals with Type I diabetes. The major problem in obtaining successful transplants has been to manipulate the immune system to accept the graft without activating the autoimmune system that can destroy the graft. Unlike kidney and heart transplants that seek tissue immune compatibility between donor and host, this compatibility targets the islet cell transplant to destruction by the very autoimmune mechanisms that heralded the onset of diabetes in the first place. Attempts are now being made to "clear up" the donor tissue of the kinds of cells that initiate immune responses and to identify sites in which the donor tissue can be transplanted to protect it from immune destruction.

Techniques of modern molecular biology are allowing detailed elucidation of the structure of key genes for diabetes, in particular the insulin gene and the insulin receptor gene. One goal is to identify what genetic elements, if any, may be associated with Type II diabetes, noninsulin-dependent diabetes. The identification of the gene for the insulin receptor has been very recent, but already this knowledge has allowed examination of the functional elements of the insulin receptor. We have learned that insulin binds to a specific insulin receptor at the cell surface. Once bound, insulin is transported into the cell and degraded while the receptor is recycled to the cell surface. We are trying to identify other biochemical events that correlate with the processing of the insulin receptor complex. We have recently found, for instance, that the insulin receptor itself is chemically modified by phosphorylation after insulin binds. We know that in insulin sensitive cells, a glucose transporter is recruited from the interior of the cell to the cell surface. We hope that as we find out more about the biochemical alterations that follow insulin binding, we can not only understand specifically how insulin controls carbohydrate, lipid, and protein metabolism, but can also find the defects that account for the insulin resistance characteristic of Type II diabetes.

ISLET CELL TRANSPLANTATION

Mr. Early. The justification states that plans are being developed to facilitate the procurement and processing of human

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islet tissue, and to establish a patient transplant registry. Where are you now in this endeavor, and what sort of a time frame are we looking at until this registry could be operational?

Dr. Renault. The NIDDK recognizes its leadership role in stimulating and promoting the multidisciplinary research necessary to develop further knowledge and techniques needed to make transplantation a viable treatment for diabetes. Research on islet cell transplantation is encouraging but several technical problems, including rejection of the transplanted tissue and determining the ideal site for the transplant, must be overcome before attempting to transplant islet cells in a large number of people. With large scale application of pancreas transplantation techniques, a registry would be warranted and would provide a resource to compare different strategies and methods.

The National Diabetes Research Interchange (NDRI, partially supported by a contract from NIDDK) has successfully established a pilot network for procurement of pancreatic tissue that has greatly increased tissue availability for researchers. NIDDK is developing plans for expanded collection and processing of pancreases along the lines of the NDRI pilot. However, at the present time, the highest priority research needs for these tissues are being met. Expanded efforts to collect and process tissues will be pursued when research results suggest that pancreas cell transplantation techniques should be applied on a large scale.

KIDNEY-UROLOGY CENTERS

Mr. Early. I understand a report endorsing the scientific feasibility and appropriateness of kidney-urology centers is being prepared. Would you tell us now, briefly, what the highlights of the report are?

Dr. Renault. We were happy to prepare and supply to the Committee, as requested, a report evaluating the proposal to establish up to six multidisciplinary, interinstitutional kidney-urology centers. As you know, centers have been proposed in hypertension and the kidney, diabetes mellitus and the kidney, obstructive and hereditary diseases of the urological system and kidney, nutrition and the kidney, immunology and the kidney, and cellular injury and the kidney.

Highlights of that evaluation include:

- The health problems in kidney/urologic diseases, including end-stage renal disease (ESRD) and benign prostatic hyperplasia, are enormous, and current treatment approaches are only palliative. We would expect the incidence of ESRD to be reduced through this mechanism.
- Research opportunities are exciting and promising.
- Research needs and opportunities exist.

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- The specialized research centers mechanism offers unique opportunities for multidisciplinary and interdisciplinary research.

- The kidney and urologic diseases research centers concept has been strongly endorsed by professional and lay groups in these fields, and is consistent with recently enacted NIH authorizing legislation.

Mr. Early. What would the cost of establishing a center be?

Dr. Renault. The estimated cost for establishing a center in kidney and urologic diseases research is estimated at $800,000 to $1,000,000.

Mr. Early. What would be the optimal number of centers you would like to establish in the first year of such a program?

Dr. Renault. Six research areas have been identified by the Committee, as I noted earlier, and we would like to establish at least one center in each area. We would expect that the establishment of at least six centers would ensure that the objective of reducing the incidence of ESRD could be realized.

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DIABETES--LONG RANGE PLAN TO COMBAT DIABETES

Mr. Hoyer. Director, December 10, 1985, was the 10th Anniversary of the adoption of the "Long Range Plan to Combat Diabetes." What kind of grade would you give Congress and the research community concerning the implementation of the recommendations included in the plan?

Dr. Renault. I believe that both the Congress and the research community have been very responsive in implementing the recommendations contained in the "Long Range Plan to Combat Diabetes" that was developed by the National Commission on Diabetes.

Mr. Hoyer. What are the challenges that lie ahead?

Dr. Renault. Although we have made considerable progress in our understanding of the etiology, pathogenesis, and natural history of both major forms of diabetes, we have not yet established a sufficient knowledge base to either develop optimal methods for the diagnosis and treatment of these diseases and their chronic complications or to assure their cure and prevention within the forseeable future. These are the major challenges that lie ahead.

Mr. Hoyer. Are researchers close to finding a cure for Type I diabetes?

Dr. Renault. I think we have made major strides in this direction during the past decade. In particular, advances in immunology, genetics, and in related areas of cellular and molecular biology are now providing new and important insights into both the causes of Type I diabetes and the various changes that are associated with the early onset and subsequent progression of this disease. Limited clinical studies are already underway in a few centers to assess the potential benefits and risks associated with immunosuppression during the period immediately following clinical onset. Major advances have also occurred in the development of techniques that now permit the successful transplantation of insulin-producing cells into animal models of Type I diabetes, with subsequent resolution of their insulin dependence. However, a cure for Type I diabetes in humans has not yet been developed. Although recent progress in this area has been very impressive, it is not yet possible for experts to predict how close we really are to actually achieving this goal.

Mr. Hoyer. In recent years in order to meet Congressional requirements that certain number of grants be funded, the National Institutes of Health (NIH) has negotiated downward the amounts paid per grant. On average, in order to meet the targeted number of grants, what percentage reductions in average grant size have been implemented? What kinds of reductions do we expect for 1986 and 1987? At what point do reductions affect the science being purchased?

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Dr. Renault. For the past several years we have had to reduce each of our grants an average of about four percent. Under the 1986 Revised Estimate, we project average reductions of about 10 percent and for 1987 we estimate that reductions of 14 percent will be required. It is our judgement that reductions of more than five or six percent have a significant impact on the quality and the depth of the proposed research studies.

Mr. Hoyer. Public Law 99-158, the Health Research Extension Act of 1985, authorized the division of the NIADDK into the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute of Diabetes and Digestive and Kidney Diseases. Has the division of the old institute resulted in the loss of any program money for the residual diabetes institute? Are there any adverse impacts on the NIDDK as a result of implementation of this public law?

Dr. Renault. There has been no impact on the program funds of the NIDDK as a result of the split, however, our central management staff offices have had problems trying to support two separate institutes.

Mr. Hoyer. We understand that the Office of Management and Budget (OMB) has implemented a system of more strict oversight over the management of the individual institutes of the National Institutes of Health (NIH) last fall. We understand that part of this so-called "micromanagement" has eliminated the Institute's flexibility to apportion and allot funds to individual mechanisms such as research and training, as the science dictates. What, exactly, is the nature of this OMB oversight? How has this new OMB involvement in the budgetary process affected the Institute's ability to manage programs? How has OMB's involvement affected the institute's flexibility for rebudgeting in order to fund meritorious science and training awards?

Dr. Renault. The OMB has instituted a new apportionment process based on the NIH mechanism structure. NIH is required to submit an operating plan at the beginning of the year. In general, any deviations of more than three percent must be approved by OMB. This process has increased the amount of effort required to effect a reallocation by adding an additional review.

NEW DIABETES INITIATIVES

Mr. Hoyer. What ongoing diabetes initiatives will be curtailed under the President's FY 1987 budget?

Dr. Renault. Under the President's FY 1987 budget, the Institute will be able to pursue all of its highest priority ongoing initiatives. However, the following ongoing diabetes initiatives will be selectively curtailed:

o Prevention of juvenile diabetes - This is a contract program which involves the production, characterization, and distribution of the BB/W rat, an animal model of juvenile-onset diabetes;

o Prevention of diabetic kidney disease - This is a comprehensive study which includes a clinical trial to assess the effects of intervention strategies on the progression of diabetic renal decrease in the Pima Indians, who have a very high incidence of maturity-onset diabetes;

o Minority health - This initiative includes an epidemiology study of the incidence of maturity-onset diabetes and renal disease in minority populations as well as physician education activities to emphasize the seriousness of these diseases in minority populations;

o Patient and professional education - This represents a contract program for support of the National Diabetes Information Clearinghouse; and

o Scientific instrumentation - This program supports the purchase of moderately priced scientific instruments which will be shared by two or more established investigators for studies including diabetes, endocrinology, and metabolic diseases.

Mr. Hoyer. What new initiatives have been postponed or deferred as a result of the President's FY 1987 budget and the FY 1986 Gramm-Rudman reductions?

Dr. Renault. The Institute will be able to pursue all of its highest priority new initiatives under the President's FY 1987 budget. However, we are now planning to postpone or defer the following new diabetes initiatives:

o Interdisciplinary Studies In Diabetes and Endocrinology - This initiative would increase the number of Diabetes/Endocrinology Centers in order to expand the availability of shared core laboratories and related resources to additional institutions which have strong research programs;

o Endocrine Tissue Transplantation - This is a major new initiative to capitalize on recent research advances related to the transplantation of pancreatic islet cells as a potential cure for insulin-dependent (juvenile onset) diabetes;

o Human Tissue Resources - This initiative would significantly expand current support for the procurement and distribution of human tissues for use in biomedical research and organ transplantation related to diabetes, endocrinology, and metabolic diseases;

o Nephrologic Component for the Diabetes Control and Complications Trial - This clinical study would assess the benefit of early intensive treatment of insulin-dependent diabetes on the development and progression of diabetic nephropathy;

o Diabetes Data System - This initiative would support the collection, storage, analysis, retrieval, and dissemination of data derived from patent populations with diabetes, as authorized by P.L. 99-158, the Health Research Extension Act of 1985;

o Assessment of Diabetes Mortality - This initiative would analyze the rates and causes of death among diabetics in the WHO Multinational Study of Diabetes Mortality; and

o Treatment of Diabetes - This initiative would assess current practices of physicians that relate to the treatment of people with diabetes in the U.S.

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CHRONIC RENAL FAILURE

Mr. O'Brien. What are the potentials in research for the prevention of chronic renal failure?

Dr. Renault. The potentials for research for the prevention of chronic renal failure are at the highest point in the history of nephrology. As a result of many advances in the basic research on the normal kidney and on kidney diseases we have tools available to begin both clinical intervention studies and early detection trials. These areas have a solid scientific base with very promising preliminary results in patients. The diseases which await development of proposals and support are:

1. Prevention of the progression of the nephropathy of diabetes mellitus and immunologically-mediated renal diseases leading to kidney failure. Kidney function in patients with chronic renal disease inexorably proceeds to end-stage renal failure. After a critical reduction in kidney mass due to disease, there occurs a self-perpetuating destructive process. The common denominator is that the remaining normal tissue must assume the work of the diseased parts. Thus this normal tissue is exposed to increased blood flow and increased blood pressure. These hemodynamic alterations exert a profound influence on the initiation and in the progression of glomerular scarring. Unfortunately, the current treatments do little to interrupt these mechanisms. The result is a vicious cycle with an increasing work load on kidneys which have a decreasing reserve.

Recently, investigators have found that this cycle can be interrupted and progression halted by lowering the work load on the kidney through diet and currently available drugs. In fact, the initiation of kidney disease in diabetes mellitus can now be prevented by similar treatment. These data come from animal studies and preliminary reports in humans.

Due to the impact of this problem on the health of the nation and the overall health budget, initiation of these studies is of the highest priority.

2. Early diagnosis of polycystic kidney disease using molecular biologic approaches. A new discovery will allow physicians to determine which patient has the gene which leads to this disease. Armed with this information, researchers can now design studies to prevent the formation of cysts as well as to understand their basic pathogenesis. Prior to this time physicians knew only that the children of patients with polycystic kidney disease had a 50-50 chance of having the disease. However, it was not possible to tell who was affected until cysts became large enough to be seen by x-ray or ultrasound. Since cysts do not reach such a large size until well into the child-bearing age, it was a burden on these families - whether or not they were actually affected. Similarly, there was no rational way to devise research strategies to prevent the disease. This has all been changed by the recent discovery of the localization of the PKD gene, allowing for a test which has an accuracy rate of 92 percent.

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Mr. O'Brien. According to Institute estimates, we spend nearly three billion dollars a year to treat patients with end-stage renal disease who require maintenance dialysis and kidney transplantations. Do you know if the cost of providing for end-stage renal disease care is increasing or decreasing?

Dr. Renault. The costs per patient are not increasing, i.e., the costs of dialysis have remained stable. However, there are two factors which lead to increasing costs for the end-stage renal disease program. First, the number of entering patients has been steadily increasing at a rate of 10 percent per year. This is due to increasing ability to deal with complications of end-stage renal disease and because the entrance criteria have undergone changes. In essence, dialysis therapy is available to all those in need of this therapy. The second reason that costs are increasing is due to our success in prolonging life with dialysis therapy. Patients on long-term dialysis have many complications both due to their initial disease and as a result of dialysis. This is particularly true in the nephropathy of diabetes mellitus. We have made significant progress in managing these complications. These data point to the need for means to prevent end-stage renal disease from developing.

Mr. O'Brien. What is the status of the studies undertaken by the Institute on the "Effect of Dietary Modification on Progressive Renal Disease"?

Dr. Renault. In September 1983, the NIH-NIADDK invited applications for Clinical Centers and a Data Coordinating Center to participate with the Institute under a Cooperative Agreement Program in a multicenter cooperative clinical study.

The following Centers were selected for participation under the chairmanship of Dr. Saulo Klahr from Washington University, St. Louis, Missouri: Beth Israel Hospital (Boston), Brigham and Women's Hospital (Boston), Harbor/UCLA (Torrance, CA), Johns Hopkins University (Baltimore), Massachusetts General Hospital (Boston), New England Medical Center (Boston), University of Iowa Hospital and Clinics (Iowa City), University of Southern California (Los Angeles) and Vanderbilt University Medical Center (Nashville). The Data Coordinating Center is located at the Cleveland Clinic Foundation (Cleveland) and the Nutrition Coordinating Center is housed at Case Western Reserve University (Cleveland).

The study is planned as follows:

Phase I.	Planning Phase (12 months)
Phase II.	Feasibility Phase (24 months)
Phase III.	Full-Scale Clinical Trial (4-5 years)
Phase IV.	Data Analysis and Reporting (1 year)

The Planning Phase (Phase I), September 1984-January 1986, resulted in the development of a Study Protocol, a Forms Manual, a Manual of Operations and an organizational structure for Phase II and Phase III. The study is now in Phase II. A limited number of patients are being enrolled. These patients will be initially characterized according to clinical, laboratory, and dietary find-

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ings and randomized into one of the dietary regimens: moderate protein diet, a low protein diet, or a very low protein diet supplemented with either essential amino acids or with ketoacid analogues. Phase II will be completed in July 1987. The results will be reviewed with special attention to patients' safety and acceptance of the various dietary interventions before a decision is made regarding whether or not the next phase should be undertaken.

Based on P.L. 92-603, NIH and HCFA jointly developed the clinical trial to evaluate the efficacy of dietary intervention in the modification of progression of renal disease. In this trial, each bureau is responsible for that part for which it is most qualified, namely, NIH conducts the scientific and medical aspects and HCFA oversees and supports the patient care costs. In theory, both agencies can thus profit maximally from this type of arrangement. In fact, this has turned out to be the case during the first part of the study, which has been completed. We believe that this represents a good model for the best use of scarce resources, especially at this time of fiscal restraint.

The NIDDK and the overseeing Committees are very pleased with the progress and achievements of the study, to date.

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DIABETES RESEARCH

Mr. Porter. In recent years, in order to meet Congressional requirements that a certain number of grants be funded, the NIH has negotiated downward the amount paid per grant. On average, in order to meet the targeted number of grants, what percentage reductions in average grant size have been implemented? What kinds of reductions can we expect for 1986 and 1987? At what point do reductions affect the science being purchased?

Dr. Renault. For the past several years we have had to reduce each of our grants an average of about four percent. Under the 1986 Revised Estimate we project average reductions of about 10 percent and for 1987 we estimate that reductions of 14 percent will be required. It is our judgement that reductions of more than five or six percent have a significant impact on the quality and the depth of the proposed research studies.

Mr. Porter. The Health Research Extension Act of 1985, P.L. 99-158, authorized the division of the NIADDK into the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMSD) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Has this change resulted in the loss of any program money for the residual diabetes institute? Has the NIDDK experienced any adverse effects?

Dr. Renault. There has been no impact on the program funds of the NIDDK as a result of the split. However, our central management staff offices have had problems trying to support two separate institutes.

Mr. Porter. What ongoing diabetes initiatives will be curtailed under the President's FY 1987 budget?

Dr. Renault. The Institute will be able to pursue all of its highest priority ongoing initiatives under the President's FY 1987 budget. However, the following ongoing diabetes initiatives will be curtailed:

(a) Prevention of juvenile diabetes - This is a contract program which involves the production, characterization, and distribution of the BB/W rat, an animal model of juvenile-onset diabetes;

(b) Prevention of diabetic kidney disease - This is a comprehensive study which includes a clinical trial to assess the effects of intervention strategies on the progression of diabetic renal decrease in the Pima Indians, who have a very high incidence of maturity-onset diabetes;

(c) Minority health - This initiative includes an epidemiology study of the incidence of maturity-onset diabetes and renal disease in Blacks and other minority populations as well as physician education activities to emphasize the seriousness of these diseases in minority populations;

(d) Patient and professional education - This represents a contract program for support of the National Diabetes Information Clearinghouse; and

(e) Scientific instrumentation - This program supports the purchase of moderately priced scientific instruments which will be shared by two or more established investigators for studies including diabetes, endocrinology, and metabolic diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

FY 1987 Budget

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NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

For carrying out [Sections 222,] *Section* 301 and Title IV of the Public Health Service Act with respect to [arthritis,] 1/ diabetes, and digestive and kidney diseases, [$569,597,000] *$418,971,000* *(Department of Health and Human Services Appropriation Act, 1986.)*

1/ Arthritis budget activity has been transferred to a newly created Institute.

National Institute of Diabetes and Digestive and Kidney Diseases

Language Analysis

Language Provision	Explanation
"For carrying out section 301 and Title IV of the Public Health Service Act with respect to [arthritis,]....".	These activities were formerly part of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. However, they are now presented separately as a result of enactment of P.L. 99-158, a major provision of which directed the establishment of the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Amounts Available for Obligation 1/

	1985	1986 Revised Estimate	1987 Estimate
Appropriation	$543,576,000	$569,597,000	$418,971,000
Enacted administrative reduction	---	-257,000	---
Sequester order	---	-24,482,000	---
Proposed rescission	---	-7,980,000	---
Subtotal, adjusted appropriation	543,576,000	536,878,000	418,971,000
Comparative transfer to:			
National Institute of Arthritis and Musculoskeletal and Skin Diseases for establishment of new institute	-108,808,000	-109,788,000	---
National Cancer Institute for changes in the Services financing mechanisms and formulas	-2,723,000	---	---
Subtotal, adjusted budget authority	432,045,000	427,090,000	418,971,000
Unobligated balance, start of year	---	3,213,000	---
Unobligated balance, end of year	-3,213,000	---	---
Unobligated balance, lapsing	-864,000	-616,000	---
Total, obligations	427,968,000	429,687,000	418,971,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1985 -- $127,000; 1986 -- $1,098,000; 1987 -- $1,098,000.

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Mechanism
(Dollars in thousands)

Research Grants	1986 Appropriation 1/ No.	1986 Appropriation 1/ Amount	1986 Available After Sequestering 1/2/ No.	1986 Available After Sequestering 1/2/ Amount	1986 Revised Estimate 1/2/ No.	1986 Revised Estimate 1/2/ Amount	1987 Estimate No.	1987 Estimate Amount
Research projects:								
Noncompeting	1,407	$218,322	1,407	$208,934	1,407	$208,934	1,361	$207,080
Administrative supplemental	(66)	4,338	(66)	4,151	(66)	4,151	(46)	1,436
Competing:								
Renewal	329	60,819	329	58,274	289	54,238	290	51,449
New	303	36,275	303	34,756	270	32,349	271	31,018
Supplemental	5	189	5	182	5	169	5	160
Subtotal, competing	637	97,283	637	93,212	564	86,756	566	82,627
Subtotal, research projects	2,044	319,943	2,044	306,297	1,971	299,841	1,927	291,143
Research centers:								
Specialized/Comprehensive centers	31	25,367	31	24,275	31	24,275	31	23,682
Other Research:								
Research career programs	171	11,459	164	10,966	164	10,966	160	10,692
Minority biomedical research support	(16)	1,250	(15)	1,196	(15)	1,196	(15)	1,196
Other research related	27	1,467	26	1,405	26	1,405	26	1,405
Subtotal, other research	198	14,176	190	13,567	190	13,567	186	13,293
Total, Research grants	2,273	359,486	2,265	344,139	2,192	337,683	2,144	328,118

Training								
Individual awards								
Noncompeting	88	2,172	88	2,172	88	2,172	90	2,216
Competing								
Renewal	---	---	---	---	--	---	---	---
New	33	813	32	785	32	785	26	640
Subtotal, individual	121	2,985	120	2,957	120	2,957	116	2,856
Institutional awards								
Noncompeting	655	14,773	655	14,773	655	14,773	651	14,650
Competing								
Renewal	102	2,301	73	1,627	73	1,627	55	1,249
New	24	541	16	357	16	357	13	289
Subtotal, institutional	781	17,615	744	16,757	744	16,757	719	16,188
Total, training	902	20,600	864	19,714	864	19,714	835	19,044
Research and development contracts	33	9,618	32	8,793	32	8,793	30	8,393
					FTEs		FTEs	
Intramural research		52,291		50,042	431	50,042	431	49,980
Research management and support		14,060		13,455	169	13,455	169	13,436
TOTAL		456,055		436,143	600	429,687	600	418,971

1/ Reflects an enacted administrative reduction of $229,000 and a carryover in unobligated funds of $2,545,000.

2/ Reflects a consultant services (Section 515 of the Treasury-Postal Service Appropriation Act, 1985) withholding of $411,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

CROSSWALK - 1986 Appropriation 1/
(Dollars in Thousands)

	MECHANISM								
	Research Grants			Training Programs					
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management & Support	Total
Diabetes, Endocrinology and Metabolism.....	$163,473	$15,071	$8,325	$1,355	$8,405	$6,588			$203,217
Digestive Diseases and Nutrition......	71,778	10,296	2,306	840	4,750	1,268			91,238
Kidney Disease, Urology and Hematology.....	84,692	---	3,545	790	4,460	1,762			95,249
Intramural Research.......							$52,291		52,291
Research Management and Support....								$14,060	14,060
Total..........	319,943	25,367	14,176	2,985	17,615	9,618	52,291	14,060	456,055

1/ **Reflects an enacted administrative reduction of $229,000 and a carryover in unobligated funds of $2,545,000.**

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

CROSSWALK - 1986 Available After Sequestering 1/ 2/
(Dollars in Thousands)

	MECHANISM								
	Research Grants			Training Programs		Research and Development	Intramural	Research	
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	Contracts	Research	Management & Support	Total
Diabetes, Endocrinology and Metabolism.....	$156,508	$14,422	$7,967	$1,342	$7,995	$6,086			$194,320
Digestive Diseases and Nutrition......	68,713	9,853	2,207	832	4,519	1,119			87,243
Kidney Disease, Urology and Hematology.....	81,076	---	3,393	783	4,243	1,588			91,083
Intramural Research.......							$50,042		50,042
Research Management and Support....								$13,455	13,455
Total..........	306,297	24,275	13,567	2,957	16,757	8,793	50,042	13,455	436,143

1/ Reflects an enacted administrative reduction of $229,000 and a carryover in unobligated funds of $2,545,000.

2/ Reflects a consultant services (Section 515 of the Treasury-Postal Service Appropriation Act, 1985) withholding of $411,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

CROSSWALK - 1986 Revised Estimate 1/ 2/
(Dollars in Thousands)

	MECHANISM								
	Research Grants			Training Programs					
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management & Support	Total
Diabetes, Endocrinology and Metabolism.....	$153,202	$14,422	$7,967	$1,342	$7,995	$6,086			$191,014
Digestive Diseases and Nutrition......	67,268	9,853	2,207	832	4,519	1,119			85,798
Kidney Disease, Urology and Hematology.....	79,371	---	3,393	783	4,243	1,588			89,378
Intramural Research.......							$50,042		50,042
Research Management and Support....								$13,455	13,455
Total..........	299,841	24,275	13,567	2,957	16,757	8,793	50,042	13,455	429,687

1/ Reflects an enacted administrative reduction of $229,000 and a carryover in unobligated funds of $2,545,000.

2/ Reflects a consultant services (Section 515 of the Treasury-Postal Service Appropriation Act, 1985) withholding of $411,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

CROSSWALK - 1987 Congressional Justification
(Dollars in Thousands)

PROGRAM ACTIVITY	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management & Support	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional				
Diabetes, Endocrinology and Metabolism.....	$148,758	$14,070	$7,806	$1,296	$7,723	$5,809			$185,462
Digestive Diseases and Nutrition......	65,316	9,612	2,162	804	4,366	1,068			83,328
Kidney Disease, Urology and Hematology.....	77,069	---	3,325	756	4,099	1,516			86,765
Intramural Research.......							$49,980		49,980
Research Management and Support....								$13,436	13,436
Total...........	291,143	23,682	13,293	2,856	16,188	8,393	49,980	13,436	418,971

National Institute of Diabetes and Digestive and Kidney Diseases

Summary of Changes

1986 Current estimated obligations	$429,687,000
1987 Estimated obligations	418,971,000
Net change	-10,716,000

	1986 Base	Change from Base
Increases:		
A. Built-in:		
1. Within-grade increases	$10,500,000	+$407,000
2. Federal Employees Compensation Fund increase	80,000	+20,000
3. Unemployment compensation increase	45,000	+5,000
4. FTS rate increase	553,000	+16,000
5. Payment for centrally furnished services	17,502,000	+622,000
6. Increased costs of laboratory supplies, materials and other expenses	21,976,000	+901,000
Subtotal		+1,971,000
B. Program:		
1. Research projects:		
a. Noncompeting continuations converting from competing status	217,794,000	+85,717,000
b. Competing (new, renewals and supplementals)	82,047,000	+82,627,000
2. Research centers:		
a. Noncompeting continuations converting from competing status	20,345,000	+3,836,000
b. Competing (new and renewals)	3,930,000	+4,595,000
3. Other Research:		
a. Noncompeting continuations converting from competing status	11,287,000	+2,234,000
b. Competing (new and renewals)	2,280,000	+2,247,000
4. Individual training awards:		
a. Noncompeting continuations converting from competing status	2,172,000	+785,000
b. Competing (new and renewals)	785,000	+640,000

Summary of Changes -- continued

	1986 Base	Change from Base
5. Institutional training awards:		
a. Noncompeting continuations converting from competing status....................	14,773,000	+1,984,000
b. Competing (new and renewals)................	1,984,000	+1,538,000
6. Research and development contracts:		
a. Continuations..............	8,043,000	---
Subtotal.............		+186,203,000
Total increases....		+188,174,000
Decreases:		
B. Program:		
1. Research projects:		
a. Noncompeting continuations converting to competing status...................	217,794,000	-94,995,000
b. Competing converting to noncompeting status......	82,047,000	-82,047,000
2. Research centers:		
a. Noncompeting continuations converting from competing status...................	20,345,000	-5,094,000
b. Competing (new and renewals)................		
3. Other Research:	3,930,000	-3,930,000
a. Noncompeting continuations converting from competing status...................	11,287,000	-2,475,000
b. Competing (new and renewals)................	2,280,000	-2,280,000
4. Individual training awards:		
a. Noncompeting continuations converting from competing status...................	2,172,000	-741,000
b. Competing (new and renewals)................	785,000	-785,000

Summary of Changes -- continued

	1986 Base	Change from Base
5. Institutional training awards:		
a. Noncompeting continuations converting from competing status........	14,773,000	-2,107,000
b. Competing (new and renewals).................	1,984,000	-1,984,000
6. Research and development contracts:		
a. Continuation...............	8,043,000	-365,000
b. New........................	750,000	-35,000
7. Intramural research: Program decrease in lower priority areas........................		-1,524,000
8. Research management and support: Program decrease in lower priority areas......		-528,000
Subtotal..................		-198,890,000
Total decreases.........		-198,890,000
Total, net change......................		-10,716,000

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Activity
(Dollars in thousands)

	1986 Appropriation Amount	1986 Available after Sequestering Amount	1986 Revised Estimate		1987 Estimate	
			FTEs	Amount	FTEs	Amount
Diabetes, endocrinology and metabolism.......	$203,217	$194,320		$191,014		$185,462
Digestive diseases and nutrition........	91,238	87,243		85,798		83,328
Kidney disease, urology and hematology.......	95,249	91,083		89,378		86,765
Intramural research.........	52,291	50,042	431	50,042	431	49,980
Research management and support......	14,060	13,455	169	13,455	169	13,436
Total obligations..	456,055	436,143	600	429,687	600	418,971
Unobligated balance, start of year..........	-2,545	-2,545		-2,545		---
Unobligated balance, lapsing.	---	+411	---	+411	---	---
Total budget authority....	453,510	434,099	600	427,553	600	418,971

NOTE: All 1986 columns reflect an enacted administrative reduction of $229,000.

National Institute of Diabetes and Digestive and Kidney Diseases

Obligations by Object

	1985 Actual	1986 Estimate	1987 Estimate
Total number of full-time permanent positions.................	602	602	602
Total compensable workyears:			
Full-time equivalent employment.....	611	611	611
Full-time equivalent of overtime and holiday hours.................	4	4	4
Average ES salary......................	$66,232	$66,232	$66,232
Average GS grade.......................	9.14	9.14	9.14
Average GS salary......................	28,224	28,224	28,224
Average salary, grades est. by act of July 1, 1944 (42 USC 207)...........	35,361	35,361	35,361
Average salary of ungraded positions..	23,206	23,206	23,206
Personnel compensation:			
Permanent positions.................	$15,719,000	$16,126,000	$16,533,000
Positions other than permanent......	6,011,000	5,861,000	5,461,000
Other personnel compensation........	750,000	750,000	750,000
Special personnel services..........	1,539,000	1,539,000	1,539,000
Subtotal, personnel compensation..	24,019,000	24,276,000	24,283,000
Personnel benefits....................	3,119,000	3,081,000	3,081,000
Benefit for former employees..........	42,000	45,000	50,000
Travel and transportation of persons..	524,000	485,000	469,000
Transportation of things..............	133,000	123,000	119,000
Rent, communications and utilities....	1,369,000	1,267,000	1,226,000
Printing and reproduction.............	441,000	408,000	395,000

Obligations by Object - continued

	1985 Actual	1986 Estimate	1987 Estimate
Other services:			
Project contracts..................	$7,872,000	$8,793,000	$8,393,000
Centrally furnished services........	17,158,000	17,209,000	17,809,000
Standard level user charge.........	561,000	293,000	315,000
Other..............................	8,344,000	7,525,000	7,172,000
Supplies and materials................	7,729,000	7,155,000	6,921,000
Equipment.............................	1,760,000	1,630,000	1,576,000
Grants, subsidies and contributions...	354,897,000	357,397,000	347,162,000
Total......................	427,968,000	429,687,000	418,971,000

National Institute of Diabetes and Digestive and Kidney Diseases

Significant Items in House Appropriations Committee Reports

Item	Action taken or to be taken
1986 House Report	
Endocrine Research	
1. "The Institute is encouraged to work in cooperation with other NIH entities on endocrine research programs. The Committee requests a report no later than January 1986 on NIH-wide plans with respect to endocrine research." (page 50).	1. With the cooperation of the other NIH institutes and divisions, a comprehensive report is being prepared for transmission to the Committee.
Kidney-Urology Centers	
2. "The center concept might provide the necessary framework and mechanism for the kidney-urology community to intensify the research advances to prevent dialysis and transplant treatment for many citizens. The Committee requests an evaluation of the proposal to establish up to six multidisciplinary, inter-institutional kidney-urology centers...." (page 51).	2. A report endorsing the scientific feasibility and appropriateness of such a kidney-urology centers program is being prepared for transmission to the Committee.

National Institute of Diabetes and Digestive and Kidney Diseases

Significant Items in Senate Appropriations Committee Reports

Item	Action taken or to be taken
1986 Senate Report	
Kidney-Urology Centers	
1. "The Committee believes that the science in kidney/urology diseases has advanced to levels that suggest the Institute should give consideration to establishing centers of excellence in kidney disease...." (page 75).	1. The report requested by the House Committee will also be sent to the Senate Committee.

National Institute of Diabetes and Digestive and Kidney Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1986 Amt. Authorized	1986 Revised Estimate	1987 Amt. Authorized	1987 Estimate
Research and Investigation........	Section 301	42 § 241	Indefinite	$409,973,000	Indefinite	$399,927,000
National Institute of Diabetes and Digestive and Kidney Diseases...	Title IV	42 § 285c	Indefinite		Indefinite	
Data Systems and Information Clearinghouses..................	Title IV	42 § 285c-1	Indefinite		Indefinite	
Division Directors................	Title IV	42 § 285c-2	Indefinite		Indefinite	
Interagency Coordinating Committees......................	Title IV	42 § 285c-3	Indefinite		Indefinite	
Advisory Boards....................	Title IV	42 § 285c-4	Indefinite		Indefinite	
Research and Training Centers.....	Title IV	42 § 285c-5	Indefinite		Indefinite	
Advisory Council Subcommittees....	Title IV	42 § 285c-6	Indefinite		Indefinite	
Biennial Report..................	Title IV	42 § 285c-7	Indefinite		Indefinite	
National Research Service Awards..	Title IV Part F	42 § 288	$244,000,000 1/	19,714,000	$260,000 1/	19,044,000
Total Budget Authority..........				429,687,000		418,971,000

1/ This training authority is shared with other research training programs of the National Institutes of Health, the Alcohol, Drug Abuse and Mental Health Administration and the Health Resources and Services Administration.

National Institute of Diabetes and Digestive and Kidney Diseases

Appropriation History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1978	218,953,000	239,253,000	274,792,000	260,253,000
1979	267,246,000	287,869,000	287,869,000	302,767,000
1980	306,318,000	341,246,000	315,000,000	341,206,000
1981	363,062,000	369,677,000	369,156,000	369,462,000
1982	334,923,000 2/	384,206,000	389,663,000	368,191,000
1983	379,422,000	408,508,000	415,856,000	413,481,000
1984	426,394,000	442,255,000 3/	442,832,000 3/	460,923,000
1985	475,324,000	515,516,000 4/	545,551,000	540,165,000
1985 Proposed Rescission	-1,171,000			
1986	519,858,000	541,298,000 5/	565,924,000	453,510,000 6/
1986 Sequester	-19,501,000			
1986 Proposed Rescission	-6,456,000			
1987	418,971,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Reflects the September Amendment, the original request was $380,594,000.

3/ Excludes $19,135,000 in NRSA training programs not considered.

4/ Excludes $19,135,000 in NRSA training programs not considered.

5/ Excludes $26,730,000 in NRSA training programs not considered.

6/ Reflects a comparative transfer of $116,498,000 for the creation of the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

National Institute of Diabetes and Digestive and Kidney Diseases

Justification

	1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate		1987 Estimate	
	Amount	Amount	FTEs	Amount	FTEs	Amount
Diabetes, endocrinology and metabolism.....	$203,217,000	$194,320,000		$191,014,000		$185,462,000
Digestive diseases and nutrition......	91,238,000	87,243,000		85,798,000		83,328,000
Kidney disease, urology and hematology.....	95,249,000	91,083,000		89,378,000		86,765,000
Intramural research.......	52,291,000	50,042,000	431	50,042,000	431	49,980,000
Research management and support....	14,060,000	13,455,000	169	13,455,000	169	13,436,000
TOTAL	456,055,000	436,143,000	600	429,687,000	600	418,971,000

General Statement

In accordance with the directives outlined in P.L. 99-158, the programs of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases have been reestablished as two institutes: National Institute of Diabetes and Digestive and Kidney Diseases and National Institute of Arthritis and Musculoskeletal and Skin Diseases.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports research on many of the most serious diseases affecting the public health. The Institute supports both basic and clinical research on these diseases which include diabetes, endocrine and metabolic disorders; digestive diseases and nutritional disorders; and kidney and urinary tract diseases and blood disorders. Basic research is also conducted in such areas as endocrinology, genetics, immunology, biochemistry, virology, molecular biology, and pharmacology. Close communication between NIDDK and other NIH programs provides for a continual cross-fertilization of fundamental knowledge in these areas.

The use of new techniques of molecular genetics makes possible the identification of genetic factors associated with increased risk for developing certain diseases, definition of specific gene defects in inherited disorders, and determination of the DNA sequencing of genes coding for substances of potential therapeutic value. Research areas of particular interest include the structure and expression of insulin, synthetic production of hormones and other substances important for treatment of disease, diagnosis of certain hematologic and metabolic disorders, and HLA typing of populations at increased risk for developing diabetes.

Developments in cell biology have recently made clear that a number of infectious diseases of the gastrointestinal tract are mediated by attachment of microoganisms to the intestinal mucosal surface of the host. Evidence suggests that, in some cases, the mucosal adherence is caused by interaction between a specific component on the surface of bacteria and a specific receptor site at the mucosal surface of the host. Research now shows that specific receptors on the gastrointestinal surface of the host which mediate adherence are genetically determined and age-related, and vary at different levels of the gastrointestinal tract. These results provide a molecular basis for understanding levels of colonization, age-related onset of diseases, and resistant and susceptible host populations. As a result, a number of points have been identified at which it may be possible to interfere with early stages of infection.

In both primary and systemic glomerular diseases, immune complexes can be found in coils of blood vessels known as the glomeruli. The responsible immunologic mechanisms thus far defined involve either deposition of the immune complexes from the circulation or their formation in situ. The latter mechanism may involve binding of antibody from the circulation to a structural antigen of the glomerular basement membrane with subsequent rearrangement and aggregation into an immune complex. Alternatively, physiochemical binding of antigen to negatively charged groups within the glomerular basement membrane may cause "planting" of immunoreactants with formation of immune complexes following the binding of complementary antibody. With the discovery of the importance of negatively charged sites within the glomerular basement membrane, a new understanding of renal disease appears to be unfolding.

Development of effective therapies for the diagnosis, treatment, and prevention of diseases within the NIDDK mission requires intensive basic and clinical research into the nature and mechanisms of life processes and disease pathology. In carrying out its research mission, the Institute supports research and research training extramurally through the use of grants and contracts, and conducts basic and clinical research intramurally at its facility in Bethesda, Maryland, and at field stations in and near Phoenix, Arizona.

Overall Budget Rationale

The FY 1987 budget request for the National Institute of Diabetes and Digestive and Kidney Diseases would support the Institute's programs at a level $10,716,000 below the revised 1986 operating level.

A total of $291,143,000 will be devoted to research project grants, $8,698,000 less than in 1986. These levels will be achieved by limiting indirect costs and by negotiating direct costs downward. The request will support 566 competing project grants at an average cost of $145,984. This represents a 1.7% decrease in average costs from 1986 and a 13.5% reduction from full recommended levels. Historically, these reductions have averaged 3 to 4 percent. The request will support 1,334 regular noncompeting project grants at an average cost of $147,041 and 27 cooperative agreements for the Diabetes Control and Complications Trial at an average cost of $404,696. This represents a 0.9 percent decrease from average costs of regular research projects in 1986 and an 14.4 percent reduction from full commitment levels. Historically these reductions have averaged 1 percent.

The 1987 request will support the same number of research centers as in 1986, a total of 31. Total support will be $23,682,000, or $593,000 less than 1986 support. These levels will be achieved by limiting indirect costs and by negotiating direct costs downward. The negotiated reduction will be approximately 20% of the approved or committed levels, as compared to a 13% reduction in 1986.

Research career award programs will be supported at the full average cost and to a level very similar to 1986, decreasing by 4 awards to a total of 160. These programs, together with other research related awards, will be supported for $13,293,000.

Training programs will be supported at the full average cost, although the number of full-time training positions will decline slightly from 1986. Fellowships will receive $2,856,000 to support 116 trainees or 4 fewer than 1986. Institutional training programs will receive $16,188,000 to support 719 trainees, or 25 fewer than 1986.

Research and development contracts will receive $8,393,000 in 1987, a decrease of $400,000 from 1986. At this level 30 contracts will be administered, 2 fewer than in 1986.

Intramural research programs will be conducted at a level of $49,980,000, or $162,000 below the 1986 total. In order to cover the unavoidable costs of mandatory items, it is expected that $1,524,000 worth of program decreases will be made in lower priority areas.

Research management and support functions will be carried out at $13,436,000, or $19,000 below 1986. In order to cover the unavoidable costs of mandatory items, it is expected that $528,000 of program decreases will be made in lower priority areas.

Program Accomplishments

Diabetes, Endocrinology, and Metabolic Diseases

The NIDDK is a leader in basic and clinical research efforts on various serious diseases caused by errors of metabolism and defects in endocrine systems. These include diabetes, cystic fibrosis, thyroid diseases, and growth and reproductive disorders. In addition, NIDDK grantees have contributed valuable insights and knowledge regarding the metabolic and endocrine components of other diseases that affect the cardiovascular, musculoskeletal, and digestive systems. Research in these areas has progressed significantly during the past several years, in part as the result of recent advances in the application of genetic and immunologic techniques to the study of diabetes and endocrinologic and metabolic diseases.

Diabetes Control and Complications Trial (DCCT): Consistent with the recommendations of two independent advisory groups and the Institute's National Advisory Council, the Institute Director determined that the DCCT would begin phase III, the full-scale phase of the trial. In phase III, approximately 1,400 patients will be followed for five to seven years to determine whether strict control of blood glucose levels can prevent or ameliorate cardiovascular and other long-term complications of diabetes. This is a long-standing, critical question in clinical diabetes, and it is anticipated that the results of this study will have a major impact on the clinical management of diabetes for many years to come.

Epidemiology: Epidemiology studies are shedding light on the two main types of diabetes: Type I or insulin-dependent diabetes (IDDM), and Type II or non-insulin dependent diabetes (NIDDM). Through epidemiology, the classification of various types of diabetes has become more precise; risk factors associated with the onset of different forms of the disease are being identified and catalogued; the possibility of early intervention due to increased knowledge about risk factors and the natural course of disease is being actively pursued; and differences in diabetic complications among various diabetic subpopulations are being explored.

The National Diabetes Data Group of the NIDDK recently made a major contribution to these epidemiologic efforts with the publication of Diabetes in America, Diabetes Data Compiled 1984. Diabetes in America provides information on the demographic distribution of diabetes, the risk of developing IDDM or NIDDM and diabetic complications, the impact of the disease on the individual patient, and the effect on the health care system. Significant statistics include: the number of new cases of diabetes has declined since the early 1970s, while the prevalence of diabetes in the U.S. has increased due to a decline in the death rate from diabetes as an underlying cause; about one out of four people with diabetes does not follow any of the three standard diabetic therapies--insulin, oral medication, or prescribed diet. Diabetes in America serves as a valuable resource for government policy makers, clinicians, researchers, educators, and others involved in diabetes-related activities.

Immune Factors: Evidence has been accumulating for several years that an autoimmune component is involved in the development of insulin-dependent diabetes mellitus (IDDM). Immune system involvement in this disease has been suggested by previous studies which demonstrated islet cell antibodies present in IDDM patients; antigen-antibody complexes in the circulation of IDDM patients; and the association of certain viral infections with disease onset. Most recently, NIDDK grantees have also discovered that IDDM patients have a lower than normal level of interleukin-2 (IL-2), one of a group of substances produced by white cells that stimulates the body's immune system. Exactly how this deficiency may relate to the disease process is unknown; further research will shed light on the cause of IDDM and, possibly, various other autoimmune diseases as well.

Insulin Receptors: In a pivotal achievement in diabetes research, two groups of NIDDK-supported researchers have identified the genetic code for the human insulin receptor. Insulin must bind with its receptors (located on cell membranes) in order to be carried inside cells where it can promote metabolic activity. Knowing the structure of the insulin receptor will increase our understanding of how the receptor works, how insulin interacts with its receptors, and how defects in this process lead to diseases such as diabetes.

Dawn Phenomenon: The dawn phenomenon--a spontaneous rise in blood sugar that occurs in many diabetics in the very early morning hours--has long been a mystery for researchers and a major problem for clinicians in their efforts to control blood sugar levels. Major insights into the development of this phenomenon have been achieved by NIDDK grantees who recently discovered that such increases in blood sugar levels appear to result from increases in growth hormone levels. This discovery provides basic knowledge about how blood sugar levels are controlled, as well as opportunities for developing new, effective therapies to prevent the dawn phenomenon.

DHEA Metabolites: NIDDK-supported researchers have been working to uncover the biologic role of dehydroepiandrosterone (DHEA)--a secretion of the adrenal glands. Expanding upon the results of previous studies, these investigators tested the effects of several substances derived from DHEA on obesity and diabetes in several strains of mice. They found that severe diabetes and obesity could be prevented or slowed in certain animal strains depending upon the combination of substances given. Understanding the nature of these mechanisms would contribute to fundamental knowledge about obesity and diabetes, possibly leading to more effective therapeutic and preventive measures.

Thyroid Workshop: During the past year, leading investigators in thyroid hormone research were brought together by the Institute for the workshop "Mechanism of Action of Thyroid Hormone." This workshop presented opportunities for these researchers to apply their knowledge to thyroid research by learning about the methods and findings of investigators in related fields and presenting and discussing their own findings with researchers from other laboratories. In depth discussions on many aspects of this fast moving area of research served to inspire and focus future research efforts on thyroid hormone.

Growth Hormone Releasing Factor: In many children with growth failure due to growth hormone deficiency, the cause is the inability of the hypothalamus to produce growth hormone releasing factor (GRF), which stimulates the pituitary to produce and release growth hormone (GH). Recently, NIDDK grantees tested the effectiveness of synthetic GRF to increase production of GH. After several days of treatment with small doses of synthetic GRF given intravenously every three hours, five of six patients demonstrated higher levels of GH and another substance, somatomedin C, also involved in stimulating growth. When these studies were extended to other groups of children, increases in growth comparable to that seen with GH therapy were achieved. Because therapy with synthetic GRF promises to be safer, less costly, and more easily administered than GH, further research in this area will be actively pursued.

Calcitonin Gene: Peptide research is a rapidly moving field; scientists are discovering previously unknown peptides and increasing their knowledge of how known peptides are produced and how they work. Several NIDDK-supported investigators have studied the gene for the calcium regulating hormone, calcitonin. They discovered that this same gene that produces calcitonin in the thyroid produces another peptide, calcitonin gene related peptide (CGRP), in other tissues such as those of the nervous system. These results will heighten research efforts to discover other yet unknown peptides, and will stimulate studies on the mechanisms by which different cells produce different products from the same gene.

Human Growth Hormone Testing: NIDDK has supported production and distribution of human growth hormone (hGH) for basic and clinical research since 1963 through the National Hormone and Pituitary Program (NHPP). In April, 1985, NIDDK suspended distribution of human pituitary-derived hormones for clinical use following reports that three patients who had received preparations of hGH from the NHPP had died of a rare neurologic disease, Creutzfeldt-Jakob Disease (CJD). To assess the risk of developing CJD in other recipients, NIDDK, in collaboration with NINCDS, has arranged to test the infectivity of all available preparations of human growth hormone distributed by the NHPP. Intramural scientists in an NINCDS laboratory have acquired appropriate experimental animal models and begun to inoculate them with lots of the growth hormone to be tested. Samples from each available lot of growth hormone and other pituitary derived hormones administered to human subjects have been inoculated intracranially, intravenously, and intramuscularly. In addition, the lots of growth hormone received by patients who developed CJD will be pooled and inoculated for additional special testing. Histopathological examination will be performed on the brain tissue of all animals which die. In addition, each of the available lots of growth hormone will be examined by electron microscopy for the presence of fibrils associated with slow virus infections.

Cystic Fibrosis: Cystic Fibrosis (CF) is the most common lethal genetic disease in Caucasians. Approximately 1 in 2,000 newborns have the disease, which causes a combination of digestive and lung problems. NIDDK efforts have been successful in steadily increasing knowledge of CF in such areas as tissue abnormalities, special nutritional needs of CF patients, and therapeutic approaches. Twenty-five years ago, children with CF had a life expectancy of three to four years; today, as a result of research progress, such children can live into their twenties, thirties, and longer.

The most recent achievement in CF research is the remarkable discovery of genetic markers for the CF gene. The markers are not responsible for CF, but they have revealed that the CF gene is located on chromosome #7. Now that scientists have identified genetic markers, they have a powerful tool with which to pinpoint the precise chromosomal location of the defective gene, and then, the cystic fibrosis gene itself. This series of discoveries could eventually pave the way for improved diagnostic methods and for gene replacement or other forms of therapy.

Nobel Winners: Several of this year's Nobel laureates received support for their research from NIDDK. The corecipient for the chemistry prize received support for his work in molecular structures. The recipients of the 1985 Nobel prize for medicine are past grantees of the NIDDK. They were honored for their research into genetic factors involved in cholesterol metabolism. Their work has tremendous impact on understanding atherosclerosis and promoting research in medical genetics and cell biology.

Digestive Diseases and Nutrition

Digestive diseases are a major cause of disability due to illness in the United States. These diseases encompass disorders of the salivary glands, esophagus, stomach, liver, gallbladder, biliary tract, pancreas, small and large intestines, and anorectum. Nutrition is a vital area of investigation due to the significant role that diet and nutritional factors have in health promotion and disease prevention. The interrelationship of digestive diseases and nutrition is evidenced in many ways: nutritional factors may initiate or aggravate a digestive disease, digestive diseases may lead to nutritional deficiences, and nutritional therapy may be used to combat or prevent a digestive problem. Basic and clinical research on digestive diseases and nutrition, supported by NIDDK, have advanced knowledge of the normal and disease states relevant to these research areas.

Gallstones: An estimated 25 million Americans suffer from gallstone disease, which costs the American public $1.0 billion in surgical expenses annually. However, NIDDK-funded researchers are advancing in their knowledge of how gallstones are formed, treated, and prevented. Scientists have found several factors that contribute to stone formation. For instance, gallbladder stasis contributes to the formation of stones and is a risk factor for stones during pregnancy and in patients receiving total parenteral nutrition (TPN). In stasis, the gallbladder contracts more slowly and does not empty completely; gallstones form readily in the "sludge" that is left in the gallbladder. Animal studies show that preventing stasis can prevent stones.

For several years, researchers have been investigating methods to dissolve stones that would avoid the cost and risk of major surgery. Recently, an NIDDK grantee successfully dissolved gallstones in patients with a new nonsurgical procedure that uses a solvent called methyl tertiary butyl ether (MTBE). The technique, performed under local anesthesia, involved the placement of a catheter (a thin, flexible tube) through the abdomen into the gallbladder. Small amounts of MTBE were then injected through the catheter directly into the gallbladder. A constant flushing of fresh solvent was continued throughout the procedure. Within hours the stones in each of the patients had begun to dissolve. If such an alternative to abdominal surgery for removing gallstones can be perfected, it may result both in enormous cost savings and in a safer substitute to surgery, especially for those patients at high risk.

Peptic Ulcers: An estimated 4 million people in the U.S. suffer from peptic ulcers. The development in the 1970's of new drugs such as cimetidine, ranitidine, and sucralfate has dramatically improved the outlook for people with peptic ulcers. In fact, the number of peptic-ulcer patients requiring hospitalization for treatment of their condition dropped over 40 percent between 1970 and 1980.

A vital area in ulcer research is the role of brain-gut peptides, short chains of amino acids that are found within the central nervous system and the gut. NIDDK grantees have studied the effects of several brain-gut peptides on animals exposed to stress. Increased levels of three different peptides within the central nervous system resulted in decreased gastric acid secretion and a protective effect against the formation of ulcers. Two other peptides had the opposite effect--gastric acid secretion increased and ulcers were formed. Understanding the cellular mechanisms of responses to potentially damaging agents is expected to have important implications for prevention and therapy of ulcers.

Gluten-sensitive Enteropathy: Gluten-sensitive enteropathy is a hereditary disease that affects the lining of the small intestine, resulting in poor intestinal absorption of most nutrients, and leading to serious malnutrition. In susceptible individuals, the expression of the disease follows ingestion of foods which contain gluten, such as wheat, rye, oats, or barley. Over 98,000 people in the U.S. suffer from this disorder and must restrict themselves to a rigid diet which excludes these foods. Institute-supported scientists have determined that the critical event in developing this disease is a specific viral infection. In response to the infection, the body produces antibodies against the viral antigen. These antibodies also act against gluten however, leading to a tissue-damaging immune reaction. Such damaging immunological cross-reactions are believed to occur in other diseases. This disorder provides a unique opportunity to study the relationships between a particular antigen and the environmental, genetic, and immunologic factors that control responses to that antigen in the gastrointestinal tract.

Inflammatory Bowel Disease: Inflammatory bowel disease (IBD) refers to Crohn's disease and ulcerative colitis--chronic inflammatory disorders of unknown cause that afflict an estimated two million Americans with diarrhea and pain. Efforts to better understand and treat IBD have been successful, however, as evidenced by the fact that in 1960, over 3,000 Americans died from IBD but, by 1980, that figure had dropped to well below 800. Nevertheless, IBD remains a serious health problem and chronic disease.

NIDDK-supported scientists have been identifying and characterizing the agents that promote inflammation (and its side effects) in IBD. Two groups of compounds (prostaglandins and leukotrienes), both manufactured in the body from the same substance, may play a role in mediating inflammation. Evidence for this was obtained most recently when scientists found significant amounts of leukotriene B_4 in the colonic mucosa of IBD patients. Characterizing the agents responsible for inflammation may lead to the development of therapies to counter their effects. Alternatively, the inflammatory response may be prevented or modulated by altering the dietary precursors for prostaglandins and leukotrienes.

Mesenteric Ischemia: Acute mesenteric ischemia (reduced blood flow in the small intestine) occurs with a variety of medical conditions. This condition is difficult to diagnose in the early stage before it becomes irreversible; untreated, the ischemia can lead to peritonitis, sepsis, shock, and death. An NIDDK grantee has just developed a technique that successfully detects early ischemia in animal studies. The technique is based on the administration of a radioisotope (133 Xe) which collects in the ischemic tissue; a scan of the patient produces an image showing the location of the ischemia so that appropriate treatment can begin. Further research will evaluate the efficacy of this technique in humans.

Liver Disease: In people with hypercholesterolemia, the liver is impaired in its ability to remove a type of cholesterol (low density lipoprotein--LDL) from the circulation; elevated levels of LDL result in coronary artery disease and, in the most severe cases, death before the age of 30. Mild cases have been successfully managed by restricting dietary intake of saturated fatty acids and cholesterol. In more serious cases, NIDDK grantees have found a combination of drugs that acts to increase the uptake of LDL by the liver (thus decreasing its concentration in the blood) and also increase the conversion of cholesterol into bile acids, producing a 50 percent reduction in blood LDL levels.

Bile Production: NIDDK grantees conduct basic research on the functioning of liver cells and their production of bile. Scientists are now able to tap into the smallest channels in the liver and obtain samples of bile when it is first made by liver cells. Studies show that pairs of liver cells that line these channels demonstrate a regular pattern of contraction, suggesting communication and coordination between neighboring liver cells. Most recently, scientists using a video microscopy system have devised a method to measure the rate of bile formation in isolated liver cells. This progress will lead to further research on the liver as it normally functions as well as its response to noxious stimuli.

Obesity: In February 1985, NIADDK and NHLBI co-sponsored an NIH Consensus Development Conference on the Health Implications of Obesity. While obesity is associated with other diseases such as hypertension, hypercholesterolemia, and non-insulin dependent diabetes, studies show that the location of body fat may be just as important as the amount of fat in determining the health risks associated with obesity. Fat cells located in the upper body, especially the abdominal area, may pose a more serious threat to health than fat cells found in the thighs, hips, and buttocks. Further research on the types and the causes of obesity will be encouraged.

Another NIDDK grantee has recently examined the effect of obesity on the distribution and clearance of several types of drugs commonly used in the treatment of patients with cardiac problems, hypertension, or psychological disturbances. Patients with an increased proportion of total body fat showed a dramatic increase in the distribution of fat soluble drugs such as diazepam (Valium) and a four-fold increase in the elimination half-life of such drugs. These observations suggest that adjustments in drug dosage should be made in consideration of the clinical and nutritional state of the individual.

Malnutrition Symposium: This Institute sponsored a U.S./Japan Malnutrition Symposium to exchange information on nutrition research. Major areas identified for future research included calcium and vitamin D and bone mineralization; the metabolism and health consequences of polyunsaturated fatty acids; and the development of new techniques in nutritional assessment.

Measuring Energy Expenditure: A very useful technique in nutrition research is the ability to measure how much energy a person expends over a period of days. Previously, this could only be accomplished by methods that were inaccurate or confining for the patient. Now, an NIDDK grantee has refined a technique that measures energy expenditure accurately and under free living conditions. The technique requires patients to ingest specially prepared water made from stable (non-radioactive) isotopes of oxygen and hydrogen and provide periodic urine collections. The development of this technique will greatly extend studies of normal adults on various diets, and studies of people with diabetes, inflammatory bowel disease, trauma, and other conditions in which the proper metabolism of nutrients is vital to maintaining and restoring health.

Vitamin D and Osteoporosis: Osteoporosis affects 15 million inidviduals, primarily postmenopausal women, and causes spinal crush fractures, hip fractures, and fractures at other sites. This disease is a major underlying cause of bone fractures in postmenopausal women and older persons in general. Researchers have discovered that a metabolite of vitamin D in daily doses of as little as 0.5 micrograms increases trabecular bone volume, improves calcium retention, and decreases bone fracture rate in postmenopausal osteoporotic women. Treatment of postmenopausal women with estrogen caused a 30-40 percent elevation in circulating levels of this vitamin D metabolite and corresponding increases in calcium absorption. NIDDK has been at the forefront of research in this area: the vitamin D metabolites have been isolated, identified, and chemically characterized under NIDDK support. They are currently being used for the treatment of a variety of metabolic bone diseases.

Kidney, Urologic and Hematologic Diseases

The NIDDK supports research efforts directed at understanding the normal and pathological structure and function of the cells and tissues of the kidney, urinary tract, and blood. Through advances in basic research, scientists are closer to defining and characterizing the causes of several diseases that affect these organs such as end-stage renal disease, glomerulonephritis, acute renal failure, urinary tract infection, benign prostatic hypertrophy, kidney stone disease, anemias of different origins, and disorders of blood cell production. This research will lead to prevention of these disorders and the development of alternative, more effective, and less costly therapies.

Kidney Transplantation: The two fundamental problems in kidney transplantation are to provide the most accurate matching of the donated organ and the patient, and to suppress the recipient's immune system to minimize rejection of the engrafted tissue. NIDDK-supported researchers have reported research results that address and, in many cases, overcome these problems. Blood transfusions given to patients before transplantation have been shown to improve the survival of the transplanted kidney in poorly matched living donor-recipient pairs. When the transfusion is combined with drugs which suppress the immune system (immunosuppression), graft survival is further improved. The exact mechanism(s) responsible for the beneficial effect of pre-transplant blood transfusions is not well understood. However, the improved results in both living related and unrelated renal transplant recipients are similar and approach those of well-matched related transplants. This is an exciting advance since it promises not only to increase the chance of prolonged function of renal transplants in recipients, but it also offers the possibility of making transplantation available to patients previously denied this therapeutic modality because of incompatibility with certain donors.

A second important advance in this field is the preliminary evidence that the use of monoclonal antibodies in kidney transplantation reverses ongoing kidney rejection and results in significantly increased graft survival. Monoclonal antibodies are molecules which are specific for certain proteins, in this case for the immune cells which are responsible for rejection. In a multicenter prospective trial in the U.S. and Europe of patients with acute renal transplant rejection, the kidney rejection reversal rate with one monoclonal antibody has been approximately 90 percent. This represents a significant improvement over other treatment modalities. The first monoclonal antibody tested had some side effects, however, and other monoclonal antibodies are now being evaluated.

Polycystic Kidney Disease: This disease represents the most frequent lethal gene in the U.S. population. It affects nearly 400,000 Americans and one in 1,000 people carry the gene. One-half of the offspring of affected parents will be affected and will pass on the gene to their children. The disease is characterized by the insidious development of kidney cysts, with progressive destruction of kidney function. Unfortunately, this disease is often not apparent prior to child-bearing age; therefore, genetic counseling has not been possible. In addition, the design of therapeutic trials has not been feasible, since the chance of a person at risk actually carrying the gene is no more than 50%. Recently, however, scientists have pinpointed the location of the defect to a specific chromosome. This breakthrough has two major benefits. First, a diagnostic test is now available to determine not only who is affected, but also who is not. Secondly, with these data in hand, researchers can now proceed to determine the exact nature of the biochemical defect and pursue clinical trials to retard or prevent the development of cysts. Thus, for the first time, there is the real possibility of preventing one of the major causes of chronic renal disease.

Kidney Stones: Kidney stone formation is one of the most common disorders of the urinary tract. An estimated one to five percent of the U.S. population will develop stones at some point in life. Two thousand Americans are hospitalized each year for kidney stones. They are a complication of a wide spectrum of disorders including metabolic disturbances such as gout, as well as urinary tract infection and misuse of certain medications. Two recent advances have sharply reduced the need for surgical removal of stones. First, shock-wave lithotripsy therapy to destroy already formed kidney stones is now available in many regions of the U.S. Secondly, studies have shown that the drug, potassium citrate, inhibits stone formation. This is an inexpensive and very effective treatment. Other NIDDK scientists have advanced fundamental understanding of the physical chemistry of the crystallization process. This new knowledge may pave the way to more effective therapies.

Urinary Tract Infections: Kidney infections are a significant health risk. In patients with end-stage renal disease, urinary tract infections account for the renal failure of 12 percent of the adults and 25 percent of the children. It is estimated that at least 8,000 deaths occur each year as a result of infections confined to the kidney. These infections are particularly menacing because they are difficult to detect and treat, and they have a tendency to recur. The most common offending organism is *E. coli*. NIDDK grantees have discovered that immunization with this bacterium, via the vaginal route in primates, appears to provide protection against urinary tract infections. This research finding is of great importance since urinary tract infections are the second most common bacterial disease observed in clinical practice and also because vaginal immunization affords protection against the relapses so characteristic of urinary tract infections.

A second group of NIDDK-supported scientists has reported isolation of a specific receptor which is responsible for the adherence of the fimbriated form of the bacterium *E. coli*. This form has tentacle-like projections which bind to the specific receptors in the urinary tract allowing the bacteria to adhere, multiply, and thus cause kidney infections. Research suggests that a certain density of receptors is required to facilitate attachment and may differentiate those patients with and without infection. These advances in knowledge about urinary tract infections are particularly timely, given the frequency, morbidity, and potential life-threatening effects of urinary tract infections.

Aplastic Anemia: Aplastic anemia is a progressive and usually fatal disease which typically results from an unexplained failure of the bone marrow to produce blood cells. In the past, it had been assumed that this disease completely destroyed the bone marrow and that the only treatment available was replacement of the failed marrow with a bone marrow transplant from a compatible sibling donor. Unfortunately, many patients who develop this disease do not have a compatible donor available to them, and other procedures are necessary. NIDDK-supported scientists have now opened a new avenue of treatment with an agent to suppress the immune system and restore normal bone marrow function in some patients with aplastic anemia. Research findings suggest that bone marrow failure is not complete or irreversible, and may be due to an autoimmune response. This advance not only affords the possibility of a cure to a group of patients for whom no other treatment is available, but also provides an opportunity to study normal bone marrow function and how it may go awry in disorders such as aplastic anemia.

Cloning of Erythropoietin Gene: Erythropoietin is a hormone which regulates the production of red blood cells by the bone marrow. Erythropoietin is produced by the kidney in response to certain stimuli--primarily alterations in oxygen delivery. The 70,000 patients in the U.S. who have chronic renal failure also have a loss of erythropoietin synthesis and therefore develop anemia. A major advance in this field has been the cloning of the human gene for erythropoietin and the production of erythropoietin from these clones. This significant achievement results from collaborative studies involving NIDDK grantees and a commercial company. The availability of erythropoietin in commercial quantities will provide the possibility of improving the quality of life and productivity of patients with this deficiency.

Intramural Research

The Division of Intramural Research pursues investigations within the Institute's laboratory and clinical facilities in Bethesda, Maryland, and Phoenix, Arizona. Intramural research activities encompass a wide range of clinical studies on arthritis and rheumatic diseases, metabolism, endocrinology, hematology, digestive diseases, diabetes, and genetics; theoretical mathematical modeling of biological problems; and multidisciplinary, fundamental research in molecular biology, pathology, pharmacology, and biochemistry, as well as biologically oriented studies in chemistry and physics. Great strides have been made in these areas and the following include a few, selected highlights of research advances from these laboratories.

Chronic Diseases in the Pima Indians: The NIDDK has supported a wide range of studies on the Pima Indians, a tribe in Arizona, for the past 20 years. The Pima Indians have the world's highest frequency of noninsulin-dependent diabetes mellitus and a high prevalence of kidney failure, gallbladder disease, obesity, and rheumatoid arthritis.

Overall in the United States, diabetes affects about 7 percent of the population aged 20 to 74 years, compared in the Pima population to 32.5 percent of the males and 39.6 percent of the females in the same age range. About 40 percent of men between the ages of 45 and 74 years, and 68 percent of women between the ages of 55 and 64 years have diabetes, the peak years for the disease in Pimas. A major cause of morbidity and mortality in diabetes is kidney disease, specifically diabetic nephropathy, and this is a serious health problem for the Pimas. The NIDDK is continuing a major clinical study of diabetic nephropathy in this population, including research on the natural history, epidemiology, and pathogenesis of renal disease in diabetic and non-diabetic Pimas.

In addition to characterizing the disease, researchers are learning more about the risk factors for developing diabetes. Phoenix studies have documented the influence of many factors on the pattern of diabetes occurring in the Pima Indians: age, family history, the presence of certain genetic markers, obesity, and response to consumed glucose. Also, long-term studies of diabetes and heart disease have shown clearly that, as in other populations, diabetes in the Pimas increases the risk of heart disease. The Pima Indian pregnancy study has determined that diabetes during pregnancy is associated with increased rates of infant death and increased rates of pregnancy complications. In addition, children whose mothers had diabetes during pregnancy were at higher risk of developing diabetes than those whose mother did not develop diabetes until later. Research in the Pima population has identified an inherited genetic marker whose presence increases the risk of diabetes.

Gallbladder disease is another serious problem for the Pima population. Overall, 45 percent of the Pima men and 75 percent of the women age 35 years and over have evidence of gallbladder disease. The NIDDK initiated a gallbladder disease survey in 1968 and has been actively pursuing research in this area. Subsequent follow-up has shown that clinically diagnosed gallbladder disease in women is related to the number of pregnancies and obesity, and is more common in both men and women with diabetes and impaired glucose tolerance than in those with normal glucose tolerance.

The Pima Indians are a unique population for research studies for several reasons, including the fact that their gene pool has been preserved relatively unchanged for centuries. Twenty years of research in this community have provided health insights that would be difficult if not impossible to produce in a less homogeneous population.

Thyroid Disease: Intramural scientists have made major contributions toward unraveling the puzzle of autoimmune diseases, in which the immune system mistakenly attacks the body's own tissue. One example is Graves' disease, a common autoimmune disorder characterized by a diffusely enlarged thyroid gland; symptoms of hyperthyroidism resulting from the overproduction of thyroid hormones; and, in some patients, eye and connective tissue complications. Intramural scientists have studied Graves' disease and characterized the disturbance of the immune system which results in the production of autoantibodies that bind to the thyroid, stimulate its activity, and thereby induce a hyperthyroid state. Continued research to characterize the multiple autoantibodies present in patients with Graves' disease may have important diagnostic and therapeutic implications for patients affected by a wide range of autoimmune diseases.

Diabetes: Two of the earliest events when insulin acts at its target cells are (1) insulin binds to its receptor, and (2) the combination activates an enzyme essential to carrying insulin's vital message to the cell. NIDDK scientists have played a key role in elucidating these two early steps in insulin action, information that is critical to exploring the disease process in diabetes. Studies are focusing on patients with two extreme degrees of insulin resistance. One group has genetic disease, with genetic defects which impair either the synthesis or function of insulin receptors. A second group has autoimmune disease, in which antibodies develop against their own receptors, secondarily causing insulin resistance. Clinical investigations of patients with extreme insulin resistance have provided critical information on the mechanism of insulin action and the nature of the disease processes in many forms of diabetes.

Glucose Transport: In other diabetes-related studies, an intramural laboratory doing basic research has provided insight into the transport of glucose in fat cells, which is stimulated by increasing the number of functional glucose transporters. These scientists have uncovered a novel mechanism for insulin regulation of this movement of glucose: insulin acts to translocate glucose transporters from a large storage pool inside the cell to the cell membrane. Glucose transport has been shown to be altered in several disease conditions, as demonstrated in animal studies of diabetes and obesity and in studies of the high-fat-fed rat and the starved rat, which all appear to share the common characteristics of insulin resistance. This research has significant implications for human diabetes, since insulin resistant metabolism of glucose is frequently observed in humans with insulin-dependent diabetes, noninsulin-dependent diabetes, obesity, and in those on diets of high fat/low carbohydrate. Understanding the mechanism through which insulin normally regulates glucose transport and metabolism may pave the way to developing new modes of treating abnormal insulin action.

National Institute of Diabetes and Digestive and Kidney Diseases

Diabetes, Endocrinology and Metabolism

1987 Authorization: Indefinite.

Budget Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987 Estimate	Increase or decrease
$203,217,000	$194,320,000	$191,014,000	$185,462,000	-$5,552,000

Purpose and Method of Operation

Basic, applied, and developmental research are fostered in the three major program areas of this Division through use of investigator-initiated research grants, center grant awards, research career development awards, and research and development contracts. National Research Service Awards support the training of individuals for full-time careers in research and/or teaching.

Diabetes

The NIDDK supports a wide range of fundamental and clinical studies on the cause, diagnosis, treatment, and prevention of diabetes mellitus and its complications. Diabetes is a heterogeneous condition whose principal feature is high levels of blood sugar. It affects an estimated 11 million Americans, or about 1 in 20 people in the United States. Long-term diabetes--even in people treated for the disease--can cause serious complications affecting the heart, kidneys, eyes, nerves, and other parts of the body. Diabetes is the fifth leading cause of death by disease in this country. Recent data indicate that the economic burden of diabetes to the country is $14 billion per year, including direct medical costs and loss of income.

Research in diabetes has wrought remarkable advances in understanding and treating one of this nation's most serious public health problems. Fundamental research studies are helping to pinpoint the roles of genetic factors, the body's immune defense mechanisms, and environmental influences--such as viral infections--in the origin and progression of diabetes. Intensive work is under way to understand, at the cellular level, abnormalities that involve not only deficiencies in insulin production and secretion, but also in processes essential to normal insulin action, such as transport mechanisms and the sequence of steps necessary for the binding of insulin to its target cells. Complementing this research are clinical efforts that have led to the development of more effective drug therapies for diabetes and to methods for better regulating blood glucose levels, such as self-glucose monitoring and the use of automated, programmable insulin infusion devices, commonly called "insulin pumps." These advances have revolutionized knowledge about the treatment of diabetes. Intensified studies are planned to exploit the many promising opportunities for further research on this complex and enigmatic disease.

Diabetes Control and Complications Trial (DCCT): The DCCT is a major multicenter clinical trial which is based on many of the recent advances in our understanding of blood glucose control in diabetes. The purpose of the DCCT is to address one of the most important questions in clinical diabetes, namely, whether strict control of blood glucose levels can prevent or ameliorate vascular and other long-term complications of the disease. In FY 1986, the trial entered phase III, the full-scale phase of the trial. Approximately 1,400 patients will be followed for five to seven years.

Centers: Many of the advances in diabetes research result from the resources available in core centers: expert consultation, availability of training in new techniques, and the availability of shared resources. Core centers provide an environment for the stimulating exchange of information between disciplines, producing innovative approaches and solutions to different aspects of research in diabetes and endocrinology. The NIDDK also supports multipurpose Diabetes Research and Training Centers, which provide a unique, multidisciplinary environment in which basic and clinical research, training, and model training-education-treatment demonstrations can flourish. The Institute maintains its commitment to supporting strong centers programs in diabetes, endocrinology, and cystic fibrosis.

Type I Diabetes Animal Model: Tremendous insights into autoimmune processes have been derived through the development and study of an animal model for Type I diabetes, the BB Wistar rat. Developed with NIDDK support, this model continues to be a source of exciting new information about diabetes. A recent study demonstrated that transfusions of whole blood from non-diabetic W-line BB/W rats into diabetes-prone rats delayed the onset of the disease up to one year. Through a series of experiments, investigators found the substance, produced by the immune system, that was responsible for delaying the onset of diabetes. This discovery provides exciting additional evidence that immune system activity contributes to diabetes. Further research on the BB/W rat will be encouraged.

Transplantation of Pancreas and Islet Cells: The destruction (from as yet unknown causes) of insulin-secreting islet cells is the basis of insulin-dependent diabetes. The theoretically straight-forward therapeutic approach of replacing those lost cells has fueled more than twenty-five years of research on islet cell function and in vitro cultivation, transplant immunology, and metabolism. Two approaches to this problem are: (1) transplanting whole sections of pancreas or (2) transplanting purified islet cell preparations. Segmental pancreatic transplantation is an experimental procedure that may prove to be a therapeutic alternative. Purified islet transplantation in human studies represents another clinical avenue toward definitive treatment of diabetes with the potential for freedom from chronic immunosuppression and for greater ease of administration. The NIDDK recognizes its leadership role in stimulating and promoting the multidisciplinary research necessary to develop further knowledge and techniques needed to make transplantation a viable treatment for diabetes. To this end, the Institute is developing plans to facilitate the procurement and processing of human islet tissue, to produce specialized reagents, and to establish a patient/transplant registry.

Paternal Role in IDDM Onset: NIDDK grantees are working to distinguish the complex environmental and genetic factors that appear to contribute to the onset of insulin dependent diabetes mellitus (IDDM). In an epidemiologic study of IDDM, investigators found that, in families with both a parent and a child with IDDM, the father is more likely to have IDDM than the mother. Other studies have looked further at the relationship between having certain genes and developing IDDM. Interestingly, the siblings of IDDM patients most often have inherited these genes from the father. This suggests that fetuses with the paternal gene have some biological advantage for survival, although they are also predisposed to developing IDDM. This work has obvious significance in terms of understanding the genetic factors involved in IDDM and identifying risk factors for this disease. NIDDK will strongly encourage continued work along all avenues that show promise of determining the cause of IDDM.

Non-Insulin-Dependent Diabetes: NIDDK grantees are attempting to uncover the primary metabolic defects that lead to non-insulin-dependent diabetes mellitus (NIDDM). One recent study has suggested a new approach for significantly decreasing the severity of the disease through continuous subcutaneous insulin infusion treatment. This research is also yielding new knowledge of insulin secretion by the pancreas. NIDDK will support continued studies to evaluate the potential clinical application of this treatment and to define further the metabolic defects associated with non-insulin-dependent diabetes.

Epidemiology: The World Health Organization's Multinational Study of Diabetes and its vascular complications is a joint effort of 14 collaborating centers around the world. Each center has collected demographic, clinical, genetic, and personal and life-style data on its diabetic patients from 1976-1978. NIDDK will support a followup study to correlate mortality data with the characteristics measured. This study will provide important data on the prognosis for death, the natural history of diabetes, and inter-country and inter-population comparisons of the complications of diabetes.

Endocrinology

Endocrine diseases are among the most common in medicine and result in an enormous impact on individual well-being and the costs of medical care. Endocrine factors also contribute to the development of other diseases such as cardiovascular disorders, cancer, and psychiatric disorders. NIDDK supports basic and clinical research on normal and abnormal functioning of the endocrine glands; the structure, function, and mechanisms of action of hormones; the effects of hormones on various processes of the body; and factors that relate to, or modify, effects of the endocrine system. This research includes investigations of specific endocrine disorders such as thyroid diseases, adrenal and pituitary abnormalities, and growth disorders in addition to the role of endocrine factors in the development of osteoporosis, digestive diseases, and other diseases. In recognition of the special importance of endocrinology to the Institute, plans are under way to charter an Endocrinology Research Program Advisory Committee to provide advice and consultation to Institute staff with respect to future program directions.

Adrenal Hormone Production: NIDDK grantees are studying the factors that influence the adrenal gland and its production of aldosterone, a hormone that regulates sodium, potassium, and fluid balance in the body. They have discovered peptides in the mammalian heart that decrease the production of aldosterone. These peptides, called atriopeptins, increase excretion of salt and water that result in lowered blood pressure. NIDDK encourages work in this field because of the tremendous implications for understanding the endocrine regulation of blood pressure and, possibly, the development of new therapies for hypertension.

Hormone Distribution Program (HDP): Since 1963, the Institute has funded the collection of human pituitaries and the distribution of pituitary-derived hormones for research. The NIDDK has contributed significantly to the advancement of research in endocrinology by making available many necessary research resources. In October 1985, the Institute convened an advisory committee to address future directions of these efforts. The Committee was asked to review the need for the collection of human pituitaries and the distribution of the human and animal pituitary hormones and related products. The Committee recommended that NIDDK continue to support distribution of human and animal-derived pituitary hormones for non-clinical use; support the development of recombinant forms of hormones that are not commercially produced; and expand the inventory of products available. NIDDK will evaluate the feasibility of these recommendations and determine the best approaches for implementation. The Institute recognizes the vital role its research resources program has played in endocrinology advances and intends to continue its support of these activities in the most effective way possible.

Human Growth Hormone: The NIH, the FDA, and the CDC will initiate a full-scale epidemiologic study of recipients of pituitary-derived hormones from the NIDDK National Hormone and Pituitary Program (NHPP). The study will evaluate their health status and provide the recipients of NHPP supplied hormones with an assessment of their risk of developing a rare neurologic disease, Creutzfeldt-Jakob Disease (CJD). This study is part of a coordinated Public Health Service response to the reports of the deaths from CJD of three patients who received pre-1977 preparations of human growth hormone (hGH) distributed by the NHPP. Because of the rarity of CJD, it is believed that some preparations of pituitary-derived hGH may have been contaminated with the agent responsible for CJD. In addition to the planned epidemiology study, NIDDK and NINCDS have initiated a collaborative effort to test the infectivity of lots of hGH distributed by the NHPP. These and other efforts are being pursued under the auspices of a PHS Interagency Coordinating Committee chaired by the NIDDK.

Metabolic Diseases

The NIDDK supports a broad array of investigations on the fundamental metabolic processes of diseases within the Institute's mission. Research projects include study of membrane structure and function; synthesis of enzymes and the relationship of enzyme structure and function to metabolic processes; and normal and abnormal metabolism of carbohydrates, fats, amino acids, and other substances. Other studies look at the development, prevention, and treatment of inherited metabolic disorders such as cystic fibrosis, Hurler's syndrome, and glycogen storage diseases. Although individually uncommon (many are considered "orphan diseases"), these disorders have profound public health impacts. Approximately 30 to 40 percent of all admissions to children's hospitals are attributable to such disorders. They account for approximately one-third of all infant deaths in the United States.

Cystic Fibrosis: Research on cystic fibrosis (CF) remains an important priority for NIDDK. One aspect of this research is development of new ways to prevent, diagnose, and treat complications of this disease. Maintaining adequate nutrition is one complication because the insufficient pancreatic activity characteristic in CF leads to digestive problems. NIDDK is currently planning to address this problem through a workshop at which experts will examine ways to apply knowledge of nutrition and gastrointestinal functioning to studies of malnutrition in cystic fibrosis. Research needs will be identified and innovative approaches to nutrition therapy will be discussed as a basis for possible new initiatives in this research field.

Enkephalin Derivative: In efforts to control severe pain, physicans may administer one of several pain killers that are very effective, but potentially addictive. Recently, in a search for new pain therapies, an NIDDK grantee has synthesized an analgesic similar to natural pain control agents (enkephalins) found in the body. This new agent works in the brain in a way that does not produce addiction. Additional research will further clarify the mechanisms by which analgesics exert their effects, possibly leading to new therapies for pain.

Inherited Metabolic Diseases: Scientists have achieved great success in understanding the make-up of genes and the ability to replicate genes in the laboratory. These advances in molecular biology and genetics have already increased understanding of genetic diseases and have presented the opportunity to combat specific inherited metabolic diseases, such as Lesch-Nyhan syndrome, through gene replacement. Much basic research remains to be done, however, to pinpoint the location of defective genes on specific chromosomes, and to insert the correct gene into a host cell. This area of research is important to the development of therapies for many inherited metabolic diseases, such as cystic fibrosis. Therefore, NIDDK will continue to encourage investigators in molecular biology and genetics to submit research applications to apply their knowledge to metabolic diseases such as cystic fibrosis, and develop innovative approaches to the identification and treatment of genetic defects. NIDDK also encourages research on the role of enzymes, proteins, and cell membrane structure and function as they relate to diseases of metabolism. Advances in this research have hinged on the development and use of techniques such as monoclonal antibodies and the crystallization of proteins.

Molecular Biology: A vital portion of research in molecular biology and genetics utilizes dot-blot filters. These are filters that contain chromosomes to which pieces of DNA are added in order to map the location of genes on each chromosome. NIDDK and the Los Alamos National Laboratory are working together to develop and evaluate the use of dot-blot filters for research. Such a research tool will greatly enhance basic research in gene mapping and greatly spur research in genetic diseases.

In a further effort to stimulate and facilitate research in molecular biology and genetics, the intramural and extramural programs of NIDDK will sponsor a symposium on molecular genetics in spring, 1986. This symposium will bring together scientists working with simple biological systems such as yeasts and those working with more complex organisms to discuss and explore new approaches for targeted gene insertion. Basic research in molecular genetics, leading to clinical applications, will be advanced by novel projects expected to be generated from this symposium.

Rationale for the Budget Request

The 1987 request for this activity reflects a net decrease of $5,552,000. Of this total, $4,444,000 applies to research project grants, and $352,000 applies to research centers. These levels will be achieved by limiting indirect costs and by negotiating direct costs downward.

In addition, fewer research project grant awards will be made than in 1986, although the same number of research centers will be supported. Research career awards and research training grants will be awarded at full average costs, but a slightly smaller number of awards will be made. Two fewer research and development contracts will be awarded than in 1986.

Impact Data	1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987 Estimate
Res. proj. grants				
Number	1,020	985	985	962
Amount	$163,473,000	$156,508,000	$153,202,000	$148,758,000
Res. centers				
Number	14	14	14	14
Amount	15,071,000	14,422,000	14,422,000	14,070,000
Other research				
Number	118	111	111	109
Amount	8,325,000	7,967,000	7,967,000	7,806,000
Training programs				
Number	427	409	409	395
Amount	9,760,000	9,337,000	9,337,000	9,019,000
Research and dev. contracts				
Number	18	17	17	15
Amount	6,588,000	6,086,000	6,086,000	5,809,000
Total	203,217,000	194,320,000	191,014,000	185,462,000

National Institute of Diabetes and Digestive and Kidney Diseases

Digestive Diseases and Nutrition

1987 Authorization: Indefinite.

Budget Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987 Estimate	Increase or decrease
$91,238,000	$87,243,000	$85,798,000	$83,328,000	-$2,470,000

Purpose and Method of Operation

Basic, clinical, applied, and developmental research is fostered in the two major programs of this Division through the use of investigator-initiated research grants, program project grants, center grant awards, research career development awards, and research and development contracts. National Research Service Awards support the training of individuals for full-time careers in research and/or teaching.

Digestive Diseases

The social and economic impact of digestive diseases is enormous: disorders of the digestive tract are the leading cause of hospitalization and surgery in the U.S. Twenty million Americans are treated for some sort of chronic digestive disease each year. An estimated 200,000 people miss work each day because of digestive problems resulting in current costs of $50 billion a year in lost wages, reduced productivity, health care expenditures, and disability payments. NIDDK supports basic and clinical biomedical research and research training pertaining to the normal function, pathophysiology, and diseases and disorders of the gastrointestinal tract and associated organs.

Diarrhea: Diarrhea is a major health problem and is still a leading cause of disability in the United States. Diarrhea is not only distressing, but may be debilitating or life-threatening when it leads to dehydration and electrolyte imbalance. Although treatment should always be aimed at a specific cause, unfortunately, it is not always possible to identify the cause of diarrhea, and so symptomatic treatment may be indicated. Multidisciplinary research will be focused on the development of new medications for the treatment of "secretory diarrhea." Secretory diarrhea occurs when the intestines, which normally absorb water, begin to secrete large amounts of water. There are several types of drugs available to treat secretory diarrhea, but they all have undesirable side effects that limit their use. NIDDK grantees will work to develop new treatments for diarrhea through: the use of different forms of currently available drugs (with fewer side effects); the testing of new drugs that specifically stimulate the intestine to absorb electrolytes, thereby, also absorbing water; and the study of antimotility agents. A workshop is also planned to stimulate research on approaches to antidiarrheal treatments.

Peptides: A rapidly moving area of research related to digestion is that of neuroregulatory peptides in the gut. The gut synthesizes a number of peptides that act on the gut itself and its nervous system (the enteric plexus). An NIDDK grantee recently demonstrated that several peptides that exist in the brain and the gut are able to stimulate nerve cells from the gut. The role of gut neuropeptides in the regulation of gut secretory, motor, immunologic, and metabolic functions and the relation of these functions to other chemical mediators of the autonomic nervous system must be defined. (Along these lines, an important advance in research on gut peptides was determining that the peptide, motilin, initiates the sweeping motion through the small intestine that accompanies digestion following a meal.) In addition, the potential role of peptides as regulators of centrally-mediated functions (gut-brain and brain-gut interactions) in health and disease, particularly in functional bowel syndrome, needs to be studied. Applications of molecular biology technology to investigation of the actions of these neuropeptides at the cellular level and the synthesis of these peptides can now be pursued by NIDDK grantees.

Liver Transplantation Data Base: Liver diseases cause 25,000 deaths annually, and are responsible for an annual economic burden estimated at $10 billion. National attention has been focused on transplantation of the liver, which is the only effective treatment for many patients with several severe forms of liver disease, including biliary atresia in children. During the past few years, improvements in liver transplantation have raised the rate of survival for patients in the first year from 30 to 70 percent. Although several centers have established expertise in performing this operation, no single liver transplant center is able to accumulate sufficient data to answer many of the important research questions that would further improve these early results and the results over succeeding years. NIDDK is establishing a research data base on patients evaluated and/or transplanted at transplant centers. This liver transplantation data base will fill the need for data by providing a central point for the collection and analysis of data from many transplantation centers. Most importantly, the data base will also be a means to study liver transplantation when a clinical trial is not possible.

Metabolic Functions of the Gut: The major function of the gastrointestinal tract is to promote normal digestion and absorption of nutrients, vitamins, trace minerals, fluids, and electrolytes, in addition to synthesizing certain proteins, such as immunoglobulins, albumin and other binding proteins, trophic growth factors, coagulation factors, and mucin and other glycolipids and glycoproteins. Basic research on the metabolic functions of the gut will be encouraged toward understanding the regulation of the synthesis of these substances which are altered in various gastrointestinal disease processes. The role of gastrointestinal hormones and neuropeptides in nutrient disposition, as well as gut-endocrine tissue interactions, gut endocrine-brain interactions, and metabolic feedback, will also be investigated.

Gallstones: Current knowledge on lipid metabolism and the development of cholesterol gallstones, combined with knowledge of known risk factors for gallstones (obesity, high fat diets, high cholesterol diets, diabetes, and some drugs), forms a very strong basis for stimulating research in the prevention of stones. This type of research has implications for a variety of disciplines, as the known risk factors for stones are the same for coronary heart disease, and the prevalence of gallstones is especially high in the aged. NIDDK will encourage research efforts in this area.

Liver Tissue Distribution System: The NIDDK is instituting a system to procure, preserve, and make available to researchers liver tissue derived from diseased livers obtained after transplantation and normal livers not suited for transplantation. Such a tissue distribution system would greatly facilitate research on normal liver function and disease processes. For instance, abnormal enzymes, proteins, receptors, and other components can be purified from the organ in sufficient quantities for study, and cell cultures from livers of patients with genetic diseases may be used to develop treatments or discover genetic markers.

Liver Cell Death: Liver cell death plays a prominent role in liver disease: morbidity and mortality of liver disease are related to the extent of liver cell death; repeated episodes of liver cell death contribute to transforming chronic liver injury into the more serious condition of cirrhosis; and liver cell cancer is preceded by liver cell death. Individual liver cells can die from several causes including toxins and various reactive compounds formed from drugs. NIDDK will sponsor a workshop and encourage more research in understanding the mechanisms of liver cell death in the hope that this knowledge will lead to better methods of disease prevention and treatment.

Anorectum: NIDDK has lead responsibility at NIH for basic and applied research on anorectal diseases and disorders including hemorrhoids, fissures, fistulas, anorectal Crohn's disease, proctitis, rectal prolapse, constipation, and fecal incontinence. These conditions cause chronic discomfort and disability for many people and represent a considerable economic burden. NIDDK recently convened a group of experts in anorectal diseases and disorders, and has plans to sponsor additional workshops and advisory meetings on clinical and basic research in this area. As a first step, NIDDK will facilitate research on hemorrhoids by providing leadership in the development of standardized nomenclature for type and severity of hemorrhoids in order to enable the comparison of diagnoses and research results.

Pancreas: The pancreas is composed of endocrine and exocrine tissues. The endocrine tissue secretes hormones (such as insulin) and the exocrine tissue secretes enzymes for digestion of starches, fats, and proteins. NIDDK grantees have shown that insulin and other hormones exhibit a regulatory effect over exocrine cell functions. NIDDK plans to stimulate and expand multidisciplinary research in the relationship between the endocrine and exocrine regions of the pancreas under normal and pathologic conditions, and anticipates supporting a workshop in this area.

Digestive Diseases Centers: The research supported by NIDDK in the digestive diseases centers program is relevant to the study of the underlying causes, mechanisms, diagnoses, early detection, prevention, control, and treatment of digestive diseases and related physiological, pathophysiological, congenital, or metabolic disorders resulting from such diseases.

Each of the centers brings together basic scientists, such as immunologists and biochemists, and clinicians, such as surgeons, endoscopists, and radiologists in cooperative research efforts. The centers make possible cooperative research among these investigators by having centralized resources available for research projects and by encouraging scientists to develop new investigations and collaborations in the area of digestive diseases and disorders.

Expanded in FY 1984 and again in FY 1985, this NIDDK program now supports twelve centers across the United States which are devoted to the study of diseases and disorders of the digestive system. These centers focus their research on the liver and its diseases, normal and abnormal motility and processes of the digestive tract, diarrhea, gut hormones, and the functional morphology of the digestive tract.

The NIDDK will continue to foster this coordinated, multidisciplinary approach to research focused on digestive diseases in institutions with demonstrated research excellence and where investigators are able to work together in a coordinated and productive manner.

Epidemiology: The use of computers and new methods and techniques are increasing the range and effectiveness of epidemiological studies. The computer makes it possible to store and easily retrieve large amounts of precise data and submit this mass of data to new, sophisticated, statistical analyses that were not previously available. Other techniques such as the use of diagrams to localize lesions and digital imaging provide increasingly precise data. Voice responsive data storage techniques allow the examiner to record findings while performing an examination. Further, epidemiologists are sharpening their skill in developing and applying precise definitions of terms and procedures in clinical trials as well as in observational studies. To take advantage of the opportunity this new technology offers, a program in epidemiology and data systems in digestive diseases and nutrition is being developed.

Nutrition

NIDDK fosters and supports research in the broad areas of fundamental and clinical nutrition. Application of state-of-the-art techniques in the areas of cell biology, molecular biology, immunology, and integrative physiology is encouraged in order to increase knowledge concerning (1) the function and requirements of nutrients, (2) the relationship of diet and nutrients to health and disease, and (3) the prevention and treatment of diseases as an outgrowth of nutrition research. Clinical problems of interest to NIDDK include obesity, anorexia nervosa, diabetes, chronic renal disease, end-stage liver disease, gastrointestinal dysfunction, bone disease, total parenteral nutrition, and combined nutrient-drug interactions and management of patients.

Enteral and Parenteral Nutrition: Significant advances have been made in the area of total parenteral nutrition (TPN), a special means of providing nutrients by intravenous administration. Approximately 1,000 people of various ages are dependent on long-term use of TPN and the number is estimated to double each year.

A vital ingredient in the mixture used in parenteral nutrition is the fat emulsion which provides a large number of the needed calories and fatty acids (essential for maintaining cell membranes and producing other essential substances). The different lipids used as fat emulsions provide varying amounts and types of fatty acids including different portions of the omega-3 and omega-6 series (two different classes of essential fatty acids with different actions in the body). Because these fat emulsions are providing more and more of the total caloric intake for certain patients, and for longer periods of time, more must be learned about their effects on metabolism and function, and better fat emulsions must be developed. The results of this research would be immediately applicable to understanding lipid utilization and metabolism in the gastrointestinal tract, providing insight into the advantages and disadvantages of altering the average person's dietary intake of fats.

Obesity: More than 30 million adult Americans are considered overweight. NIDDK will further encourage basic and clinical research efforts on obesity. Studies will be supported to increase understanding of the biological mechanisms that control satiety and appetite. In addition, investigators will work to characterize the different types of obesity in order to develop methods of intervention and prevention appropriate for each type.

Clinical Nutrition Research Units (CNRUs): CNRUs have upgraded the role of clinical nutrition and the quality and quantity of clinical nutrition research in the institutions where they are located. CNRUs provide an excellent mechanism to carry out new investigations and new "pilot" projects and accomplish much of the research described above. They have stimulated progress in multidisciplinary research in clinical nutrition, enhanced patient care, strengthened training environments, and generated useful nutrition information for the public.

CRNUs provide support for a wide range of research projects, including studies of metabolic bone disease and calcium metabolism; parenteral nutrition; energy metabolism; malabsorption; growth retardation; cancer; diabetes; atherosclerosis; vitamins and gastrointestinal disease; kidney stones; nutrition, lipids, and cardiovascular disease; genetics, growth, and development; nutrition and cancer; and the use of stable isotopes, particularly as diagnostic tools. CNRUs, which have served to greatly advance knowledge in nutrition-related areas, will continue to be a major force in nutrition research.

Rationale for the Budget Request

The 1987 request for this activity reflects a net decrease of $2,470,000. Of this total, $1,952,000 applies to research project grants, and

$241,000 applies to research centers. These levels will be achieved by limiting indirect costs and by negotiating direct costs downward.

In addition, fewer research project grant awards will be made than in 1986, although the same number of research centers will be supported. Research career awards and research training grants will be awarded at full average costs, but a slightly smaller number of awards will be made. The same number of research and development contracts will be awarded as in 1986.

Impact Data	1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987 Estimate
Res. proj. grants				
Number	470	453	453	443
Amount	$71,778,000	$68,713,000	$67,268,000	$65,316,000
Res. centers				
Number	17	17	17	17
Amount	10,296,000	9,853,000	9,853,000	9,612,000
Other research				
Number	33	31	31	30
Amount	2,306,000	2,207,000	2,207,000	2,162,000
Training programs				
Number	245	235	235	227
Amount	5,590,000	5,351,000	5,351,000	5,170,000
Research and dev. contracts				
Number	8	8	8	8
Amount	1,268,000	1,119,000	1,119,000	1,068,000
Total	91,238,000	87,243,000	85,798,000	83,328,000

National Institute of Diabetes and Digestive and Kidney Diseases

Kidney Disease, Urology and Hematology

1987 Authorization: Indefinite.

Budget Authority:

1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987 Estimate	Increase or decrease
$95,249,000	$91,083,000	$89,378,000	$86,765,000	-$2,613,000

Purpose and Method of Operation

Basic, applied, and developmental research are fostered in the three major program areas of this division through the use of investigator-initiated research grants, research career development awards, and research and development contracts. National Research Service Awards support the training of individuals for full-time careers in research and/or teaching.

Kidney Disease

Kidney and urinary tract diseases and disorders are among the most critical public health problems in the U.S. These diseases affect more than 13 million Americans and account for over 80,000 deaths each year. Federal expenditures to treat the more than 70,000 patients with end-stage renal disease who require maintenance dialysis and kidney transplantations are nearly $3 billion annually. To understand and combat kidney disease, NIDDK grantees are actively exploring the normal structure and function of the kidney and selected genetic and acquired diseases of this organ. High priority areas of research include understanding immune-mediated diseases of the kidney; improving the success of kidney transplantation and maintenance therapies for end-stage renal disease patients; and understanding the disease processes in diabetic nephropathy, polycystic kidney disease, glomerulonephritis, interstitial nephritis, and acute renal failure.

Diabetic Nephropathy in the Pima Indians: A major cause of morbidity and mortality in diabetes is kidney disease, diabetic nephropathy. Diabetes is one of the leading causes of end-stage renal disease in the U.S., necessitating dialysis or kidney transplantation. The prevalence of non-insulin dependent diabetes in the Pima Indian population in Arizona is 10 to 15 times as frequent as in the general population of the U.S. The prevalence statistics are, in fact, staggering: 46% in males aged 65 to 75 years and nearly 69% in females aged 55 to 64. Significantly, the major cause of death in diabetic Pimas is the nephropathy associated with this disease. The prevalence of diabetic nephropathy and its severity are postulated to be directly related to the duration of the diabetic process itself. Epidemiologic investigations over the past 20 years have shown that clinically detectable renal disease occurs primarily in those with diabetes, whereas non-diabetic Pima Indians apparently have a low prevalence of renal disease. The NIDDK has issued a Request for Proposals for a data coordinating center to assist in a multifaceted study of the epidemiology, natural history, and pathogenesis of renal disease in the Pima Indian population. In addition, the Institute is also pursuing clinical studies to assess the effects of diet on progression of diabetic renal disease in this patient population. This study is a collaborative effort involving scientists from NIDDK intramural and extramural laboratories and will be conducted in four phases over a five year period. This study is of importance not only to the Pima Indians, but also to the general population, since many conclusions in this genetically well-defined group may have broad applicability.

Effect of Dietary Modification on Progressive Renal Disease: End-stage renal disease represents a major component of the U.S. health budget. The NIDDK has issued two Requests for Applications in the last few years to invite researchers to participate in the multicenter cooperative clinical study to define the influence of dietary modification on the progression of chronic renal disease/renal insufficiency. Specifically, this NIDDK-supported study, with collaborative funding from the Health Care Financing Administration in FY 1985-1992, is determining the effect of protein and phosphorus restriction on the rate of progression of chronic renal disease. Phase I, the development of the clinical protocol and manual of operations for the study, is completed and the collaborating centers are moving through the remaining three phases. The full trial is expected to take seven to nine years to complete and will enroll a minimum of 540 patients. The results of this study are likely to have an important impact on whether or not dietary modifications are considered pertinent in treatment of chronic renal disease in clinical practice. In addition, NIDDK is exploring the feasibility of initiating a major clinical diet study with pediatric patients. The goal of this study is to compare the effects of high and low protein intake on renal function and linear growth in a large group of pediatric patients with chronic renal insufficiency before dialysis or transplantation. The Institute intends to seek the means to prevent or delay the development of end-stage renal disease in pediatric patients, while allowing normal growth and development.

Kidney Transplantation: Substantial progress has recently been made in reducing morbidity and mortality associated with kidney transplantation in end-stage renal disease (ESRD). Advances include a better understanding of the system for matching donor and recipient tissue types; utilization of blood transfusions before transplantation to precondition potential transplant recipients; improved donor organ preservation techniques; and the use of the drug cyclosporin to suppress rejection of the transplanted kidney. The picture is far from ideal, however, for the estimated seven thousand ESRD patients who undergo kidney transplants each year. As improvements occur, patients with less well-matched organs have been offered this treatment modality since it is far preferable to chronic dialysis. Overall graft survival has improved only slightly in the past decade, however; and loss of donated kidneys due to rejection remains a major problem. The primary means to treat rejection are drugs which have serious health consequences, including increased susceptibility to infection and potential damage to the new kidney. The Institute will continue to support research studies to improve kidney transplantation efforts.

While many important research questions remain unanswered, the history of transplantation may be at a critical turning point. One of the most exciting avenues being explored is the interaction between the immune system and the kidney, and the means by which each component can be modulated. The NIDDK is encouraging research on this interaction at the molecular level, the most fundamental physiologic level. Related studies will seek to develop new and more sensitive methods to measure renal transplant rejection, and to develop new methods to suppress rejection by manipulating the molecules that cells use to communicate and proliferate. A special focus of this research will be children with end stage kidney disease. Such children face the problems of growth retardation, medication side effects more profound than in adults, and an immune system more responsive than in adults, in addition to renal failure itself. Requests for Applications have been issued by the NIDDK to stimulate investigations in two research areas: (1) probing the molecular mechanisms involved in renal transplantation, and (2) improving the outcome of renal transplantation in children. Such studies will necessitate close collaboration between basic immunologists and those responsible for clinical transplantation.

Urologic Diseases

The NIDDK supports research on the lower urinary tract and associated diseases such as urinary tract infections, neuromuscular disorders of bladder function, urinary obstruction due to benign prostatic enlargement, and kidney stone disease. These diseases affect approximately eight million Americans each year and account for about 20 percent of deaths from kidney disease. Despite the obvious importance of urologic diseases, they have not attracted a large amount of interest in either the basic or clinical research community. Expanded basic research efforts are needed to provide new knowledge of normal physiology, to identify factors that contribute to disease, and to lay the groundwork for clinical studies to develop and evaluate new and more effective therapeutic measures. This is truly a research area in its infancy. Finally, the study of sexual dysfunction in the male is an important field in which the Institute hopes to encourage greater research activity.

Benign Prostatic Hyperplasia: Benign prostatic hyperplasia (BPH) is characterized by excessive growth of the prostate gland, which can cause obstruction of urine flow. This leads to discomfort, poor control of urination, and the possibility of chronic urinary tract infection, which may cause renal failure. BPH is a near epidemic disease in men over the age of 50 and is present in 80% of men over the age of 60. The morbidity associated with BPH results in medical costs estimated to be in excess of $1.5 billion each year. The causes of BPH are unknown and no acceptable therapy is currently available to retard, reverse, or arrest prostatic growth. To stimulate interest in clinical and basic research in this field, the Institute sponsored the Second NIDDK Symposium on the Study of Benign Prostatic Hyperplasia (BPH) in FY 1985. The agenda included discussions on the endocrine aspects of BPH, prostatic growth and development, BPH pathology in humans and animals, and clinical management of prostatic obstruction. Several areas for future study were identified: the normal structure, function, and development of the prostate; the role of androgens in the development of BPH; the effect of growth of different parts of the prostate on urinary obstruction; and the development of non-surgical treatment strategies. The Institute has initiated dialogue with the research community in each of these areas by several mechanisms. This critical area will be emphasized in the coming year not only because of its current importance, but also because its significance as a health problem parallels the steadily increasing age of the United States population.

Sexual Dysfunction: Impotence is a devastating problem for a male and his sexual partner. Impotence has been thought to be due to psychological factors or the normal consequence of aging, but these postulates are increasingly being questioned as inaccurate. Professional interest in this problem broadened as it was realized that older men might have organic (and thus potentially curable) disorders as a major cause of impotence. Although sexual dysfunction may be associated with the use of certain medications or some types of vascular disease or neurologic disease (such as diabetic neuropathy), it remains largely unexplained. The NIDDK is thus promoting research to evaluate the factors that may contribute to impotence in men and to analyze the relationship between reproductive hormonal measurements and certain underlying organic problems. A related area of research in which the NIDDK hopes to stimulate interest is the problem of impotence in diabetics. An estimated 25 to 60 percent of all diabetic men will develop impotence, and reports have indicated that more than 50 percent of all diabetics are impotent 10 years after disease onset. The cause is not clear. In some cases, impotence may result from a metabolic imbalance related to poor control of the diabetes. The NIDDK intends to encourage research in the endocrine, neurological, vascular, and psychological components of impotence.

Hematologic Diseases

The NIDDK supports a broad range of basic research in hematology, including studies of hemopoietic stem cells, red blood cell structure and metabolism, hemoglobin structure and its genetic regulation, iron metabolism, and white blood cell structure and function. Disease-related research is focused on anemias caused by nutritional, genetic, or other factors; disorders of blood cell production; immune diseases such as systemic lupus erythematosus and immune thrombocytopenic purpura; and studies of histocompatibility matching in support of organ transplantation activities.

Hematin Therapy for Porphyria: The porphyrias are hereditary disorders resulting from the deficiency of a specific enzyme in the pathway which synthesizes heme, an iron compound constituting the pigment portion of the hemoglobin molecule in blood. Acute attacks in patients with these disorders include abdominal pain, muscle weakness, and neurologic problems, sometimes progressing to coma, respiratory insufficiency, and death. Despite recent improvements in management, the case fatality of acute porphyria remains high. Since the attacks are difficult to predict, preventive therapy is also difficult. The NIDDK intends to issue a Request for Proposals to test the clinical value of hematin therapy for acute porphyric attacks. Preliminary clinical evidence indicates this is an effective therapy, but no rational criteria have been developed for timing of administration, dose, drug formulation, and other key parameters. In addition, solid data are needed on potential side effects. These data can only be obtained by means of a controlled clinical study. The NIDDK intends to pursue actively the critical studies that are needed on this promising orphan drug.

Recombinant Gene Insertion into Bone Marrow Cells: For the first time, scientists have been able to alter a specific gene in human cells. This research was supported by the NIDDK. The human gene that was altered specifies the blueprint for the synthesis of hemoglobin, the oxygen-carrying protein of red blood cells. The altered hemoglobin gene is the one that is defective in blacks with sickle cell anemia. At present, bone marrow transplants from a donor with normal hemoglobin genes are the only available treatment for patients with severe hemoglobin diseases. But this is a very costly treatment and the dangers of transplant rejection are substantial, often leading to disfigurement and death. Geneticists hope to use gene replacement techniques to treat a sickle-cell patient's own bone marrow cells with a normal hemoglobin gene and then return the cells to the patient, thus circumventing the risks of transplant rejection. This important research holds the promise of a cure for a serious, disabling, and sometimes fatal disease which affects a substantial part of the U.S. population.

Rationale for the Budget Request

The 1987 request for this activity reflects a net decrease of $2,613,000. Of this total, $2,302,000 applies to research project grants. These levels will be achieved by limiting indirect costs and by negotiating direct costs downward. In addition, fewer research project grant awards will be made than in 1986. Research career awards and research training grants will be awarded at full average costs, but a slightly smaller number of awards will be made. The same number of research and development contracts will be awarded as in 1986.

Impact Data	1986 Appropriation	1986 Available After Sequestering	1986 Revised Estimate	1987 Estimate
Res. proj. grants				
Number	554	534	534	522
Amount	$84,692,000	$81,076,000	$79,371,000	$77,069,000
Other research				
Number	51	48	48	48
Amount	3,545,000	3,393,000	3,393,000	3,325,000
Training programs				
Number	230	220	220	213
Amount	5,250,000	5,026,000	5,026,000	4,855,000
Research and dev. contracts				
Number	7	7	7	7
Amount	1,762,000	1,588,000	1,588,000	1,516,000
Total	95,249,000	91,083,000	89,378,000	86,765,000

National Institute of Diabetes and Digestive and Kidney Diseases

Intramural Research

1987 Authorization: Indefinite.

Budget Authority:

1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987 Estimate	Increase or decrease
$52,291,000	$50,042,000	$50,042,000 (FTEs: 431)	$49,980,000 (431)	-62,000 (--)

Purpose and Method of Operation

Intramural activities provide many examples of outstanding research in the basic and clinical sciences, leading to important advances in medicine. Over 200 research projects, including various combinations of laboratory, clinical, epidemiological, and biometric investigations, are conducted by NIDDK scientists in facilities at Bethesda, Maryland, and at Phoenix, Arizona. Effective research strategies are ensured through close collaboration with scientists of other NIH institutes, other government agencies, and investigations in institutions throughout the United States and abroad. The following are only a small sample of intramural research activities.

Pima Indians: Over the past 20 years, the NIDDK has supported research studies involving the Pima Indians, a tribe in Arizona. This population provides researchers with a unique opportunity to study a number of serious health problems which plague this population and others as well. The Pima Indians have the world's highest frequency of noninsulin-dependent diabetes mellitus and a high prevalence of kidney failure, gallbladder disease, obesity, and rheumatoid arthritis. Important research accomplishments have been achieved from NIDDK investigations of the Pimas, particularly in the areas of diabetes and its complications, gallbladder disease, obesity, and the relationship between cholesterol and heart disease.

NIDDK scientists are actively pursuing research on a number of important health issues with the cooperation of the Pima population. Kidney disease in the Pima Indians is almost entirely related to the complications of diabetes. The Institute is supporting a research project evaluating urinary tract infection, blood pressure, and severity and type of diabetes as risk factors for the development of kidney disease.

The high frequency of diabetes in the Pimas is associated with the presence of a genetic marker. NIDDK scientists will continue research using restriction fragment length polymorphisms or sites on a fragment of a chromosome that are variable between individuals for a given trait, in conjunction with genetic linkage studies. This study is seeking the specific site of the genetic defect using DNA isolated from white blood cells of diabetic patients and their families. Once the chromosomal location is known, it should then be possible to identify the specific sequence of genes which leads to predisposition to diabetes. Other diabetes-related research includes studies of normal glucose tolerant offspring of patients with diabetes to determine the sequence of deranged metabolic events. Additional studies are needed on glucose control during pregnancy and its effect on diabetes and obesity in children. Phoenix researchers are also searching for mechanisms at the cellular level that could explain insulin resistance.

The Pima Indians have a high percentage of both men and women with evidence of gallbladder disease. The NIDDK is actively pursuing research leads which indicate a possible relationship between Indian heritage and the prevalence of gallstones. Research data also suggest that asymptomatic gallstones are not a benign condition in the Pimas and may predispose Indian women to biliary cancer. Some important questions about mortality rate need to be answered. The actual cause of death in biliary cancer patients needs to be determined as well as the effects of gallbladder surgery. Additional studies are planned by the Institute in these areas.

Obesity is frequently considered an important factor in the accumulation of high levels of cholesterol in the blood, which have long been associated with an increased risk of cardiovascular disease. The Pima Indians are an enigma in this regard. They have an extremely high prevalence of obesity but a significantly lower rate of heart disease than that experienced by Caucasians in the U.S. The NIDDK has supported research investigations in this area in the past and is encouraging future studies. The Pima Indians provide an ideal group for studying the relationships between obesity and cholesterol and how they may be related to heart disease.

In summary, the NIDDK is actively seeking answers to important research questions related to some of the critical health problems plaguing the Pima population. The focus is particularly on diabetic nephropathy, arthritis, genetics, and diabetes.

Peptic Ulcer: Two new drugs may soon be added to those now available for treating ulcers. This is good news for an estimated four million U.S. citizens with ulcers, a serious, painful, chronic disease experienced by many during their most productive years of life. Researchers in the NIDDK intramural program have reported positive results in preliminary clinical testing of these drugs. One drug, famotidine, is quite potent, has a long duration of action, and shows no adverse side effects in up to seven months of treatment. It must, however, be taken several times a day. The second drug, omeprazole, acts upon the ability of the cells in the stomach to release gastric acid. NIDDK scientists are the first in the U.S. to evaluate drugs in this class. Furthermore, omeprazole holds hope for once-a-day treatment. Preliminary results are encouraging and the Institute is actively pursuing long-term toxicity data. If these potent agents are shown to be safe, they could expand the therapeutic choices for ulcer patients.

Hepatitis: Great efforts have been devoted worldwide to identifying and characterizing the agent(s) of non-A, non-B hepatitis, which is thought to be responsible for at least 120,000 illnesses and about 1,200 deaths in the U.S. annually. An NIDDK intramural laboratory has made an important discovery in identifying the agent responsible for this kind of hepatitis. Non-A, non-B hepatitis is a difficult disease. Until now, the transmissible agent has eluded identification and diagnosis remains a process of excluding the involvement of hepatitis A virus, hepatitis B virus, and other similar viruses in the disease. This form of hepatitis may be spread by a carrier exhibiting no symptoms of the disease and occurs as a complication of blood transfusions. Institute researchers are now able to elicit the disease in disease-free primate animals. Their data indicate that the presumptive agent(s) is a retrovirus or is retrovirus-like. The next step in solving this research puzzle is to develop a blood test for the agent(s) and to screen blood before transfusions to protect blood supplies from the disease. It is also hoped that continued research to capitalize on this important finding will lead to a vaccine for protection from non-A, non-B hepatitis.

In another intramural NIDDK laboratory, patients with chronic viral hepatitis are being treated with alpha-interferon and other antiviral agents. In these studies, 40 percent of patients with chronic hepatitis B and 50 percent of patients with non-A, non-B hepatitis have responded to treatment with alpha-interferon. These two forms of chronic hepatitis are a major cause of cirrhosis and liver cancer, and there is no treatment available for either at this time. Researchers will pursue this promising treatment and explore the use of other forms of interferon as well as other antiviral agents, administered individually and in combination, in increasing the rate of response of hepatitis patients to treatment.

Vitamin D: Vitamin D is produced from cholesterol-like precursors and converted to several active metabolites. The principal metabolite is 1,25-dihydroxyvitamin D, which controls calcium transport and many other processes. NIDDK intramural scientists have been evaluating patients with both acquired and hereditary calcium deficiency which is resistant to this vitamin D metabolite. The basic and clinical research conducted by the Institute in this field has shed great light on the evaluations of these patients. Specifically, Institute researchers have documented multiple steps within the cell for deficient responses to this form of vitamin D. This research was conducted on tissue from available patients and from the marmoset, an animal model for this type of vitamin resistance. The availability of cells from these patients, plus the development of monoclonal antibodies against the receptor for this metabolite indicate that, in the future, it will be possible to analyze the gene(s) for this vitamin D metabolite receptor and determine in which patients the disorder reflects genetic change. The Institute will exploit the research avenues these findings have opened. NIDDK scientists are seeking to determine the specific effects of deficiency of this metabolite on potential target tissues, such as the immune system, the pancreatic islets, and the brain. Mild deficiency of this vitamin D metabolite occurs in many states (including aging, osteoporosis, and renal failure) as a secondary process whose importance must be determined.

Rationale for the Budget Request

The 1987 request for an Intramural Research budget of $49,980,000 reflects a net decrease of $62,000 from 1986. This represents increases of $1,033,000 for administrative mandatories and $429,000 for centrally furnished services, together with $1,524,000 in program decreases in lower priority areas.

National Institute of Diabetes and Digestive and Kidney Diseases

Research Management and Support

1987 Authorization: Indefinite.

Budget Authority:

1986 Appropriation	1986 Available after Sequestering	1986 Revised Estimate	1987 Estimate	Increase or decrease
$14,060,000	$13,455,000	$13,455,000	$13,436,000	-19,000
		(FTEs: 169)	(169)	(—)

Purpose and Method of Operation

This activity provides support for the immediate office of the Institute Director and for certain administrative and business management functions including financial management, personnel management, property control and travel audit and control, which are most efficiently performed as centralized functions. This staff continues to assume new responsibilities and reporting functions such as those required under the Freedom of Information Act and the manpower productivity measurement program.

A major portion of the resources of this activity is devoted to review and approval of grants functions, including professional and supporting personnel who are responsible for the administration of the Institute's several grants activities. Staff assists in the planning and development of programs in research, training, and fellowships that will best serve to accomplish the desired results in the areas of disease interest for which this Institute is responsible; review and evaluation of research and training grant applications for presentation to the NIDDK Advisory Council; required Council staff assistance; liaison with applicants, grantees, other components of NIH and the Department, advisory bodies, and interest organizations; and continuous surveillance of scientific information relevant to all transactions.

The other major functions under this activity are the review, management and negotiation of research and development contracts of the categorical program areas, and support of the three national advisory boards in diabetes, digestive diseases, and kidney and urologic diseases.

Rationale for the Budget Request

The 1987 request for Research Management and Support budget of $13,436,000 reflects a net decrease of $19,000 from 1986. This represents increases of $316,000 for administrative mandatories, and $193,000 for centrally furnished services, together with $528,000 in administrative cost decreases in lower priority areas.

National Institute of Diabetes and Digestive and Kidney Diseases

Detail of Permanent Positions

	1985 Actual	1986 Estimate	1987 Estimate
ES-4	23	23	23
GS/GM-15	36	36	36
GS/GM-14	53	53	53
GS/GM-13	34	34	34
GS-12	44	44	44
GS-11	38	38	38
GS-10	0	0	0
GS-09	34	34	34
GS-08	10	10	10
GS-07	58	58	58
GS-06	40	40	40
GS-05	16	16	16
GS-04	3	3	3
GS-03	2	2	2
GS-02	0	0	0
Subtotal	391	391	391
Grades established by act of July 1, 1944 (42 U.S.C. 207):			
Surgeon General Grade	0	0	0
Assistant Surgeon General Grade	0	0	0
Director Grade	25	25	25
Senior Grade	11	11	11
Full Grade	4	4	4
Senior Assistant Grade	0	0	0
Subtotal	40	40	40
Ungraded	171	171	171
Total permanent	602	602	602

THURSDAY, MARCH 13, 1986.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

WITNESSES

DR. ANTHONY S. FAUCI, DIRECTOR

DR. JAMES B. WYNGAARDEN, DIRECTOR, NIH

DR. BERNARD TALBOT, DEPUTY DIRECTOR, NIAID

DR. JOHN W. DIGGS, DIRECTOR, EXTRAMURAL ACTIVITIES PROGRAM NIAID

MICHAEL I. GOLDRICH, EXECUTIVE OFFICER, NIAID

YVONNE H. du BUY, BUDGET OFFICER, NIAID

DENNIS P. WILLIAMS, ACTING DEPUTY ASSISTANT SECRETARY, BUDGET DHHS

INTRODUCTION OF ASSOCIATES AND OPENING REMARKS

Mr. EARLY. Next we are going to hear from the Director of the National Institute of Allergy and Infectious Diseases, Dr. Anthony S. Fauci.

Dr. Fauci, if you want to tell us whom you have with you.

Dr. FAUCI. To my far left is Dr. John Diggs, Director of our Extramural Activities Program, next Mr. Michael Goldrich, Executive Officer, to my left Ms. Yvonne du Buy, Budget Officer, and to my right Dr. Bernard Talbot, our Deputy Director and Dr. Wyngaarden and Mr. Williams, whom you know. Mr. Chairman, I have submitted my written statement for the record and will spend a few minutes highlighting progress that has been made.

Last year I came before you and discussed with you the basic scientific approach in immunology and infectious diseases and how this may have important impact on the goals and directions of the National Institute of Allergy and Infectious Diseases. Today I am happy to report to you on one particular area of basic science and that is molecular biology and how this has allowed us to make major advances in several important programs. Here in Figure 1 you see a schematic diagram of how molecular biology has an impact in NIAID activities. I will briefly summarize this for you and tell you that the cloning of genes for a variety of important factors such interleukin-2 and interferon has had a major impact on our ability to manipulate the immune response by these purified immunomodulators. We have developed molecular probes to identify microbial genomes in cells leading to rapid diagnosis of infection. Investigators have characterized the receptor whereby T lymphocytes recognize specific antigens. Furthermore, the major histocompatibility complex has been precisely elucidated using molecular biological techniques. This has enormous implications for our understanding of transplantation biology. The basis for antibody diversity has been firmly established by molecular biological techniques. In addition, cloning the genes for various microbes has had important implications in the development of vaccines. For example, cloning the genes for the various stages of the malaria parasite has led to an important advance in the preparation of a malaria vaccine which is currently being tested today. The genes for hepatitis B virus have been cloned leading to the development of a second generation vaccine devoid of all of the problems of obtaining the hepatitis B surface antigen from pooled plasma samples of infected individuals. And finally, the genes for several of the proteins of the pertussis bacteria have been cloned. This will lead to important advances in developing a purified protein preparation for use as a vaccine in pertussis which would eliminate most if not all of the toxic side effects which have been such a major problem with regard to pertussis vaccine.

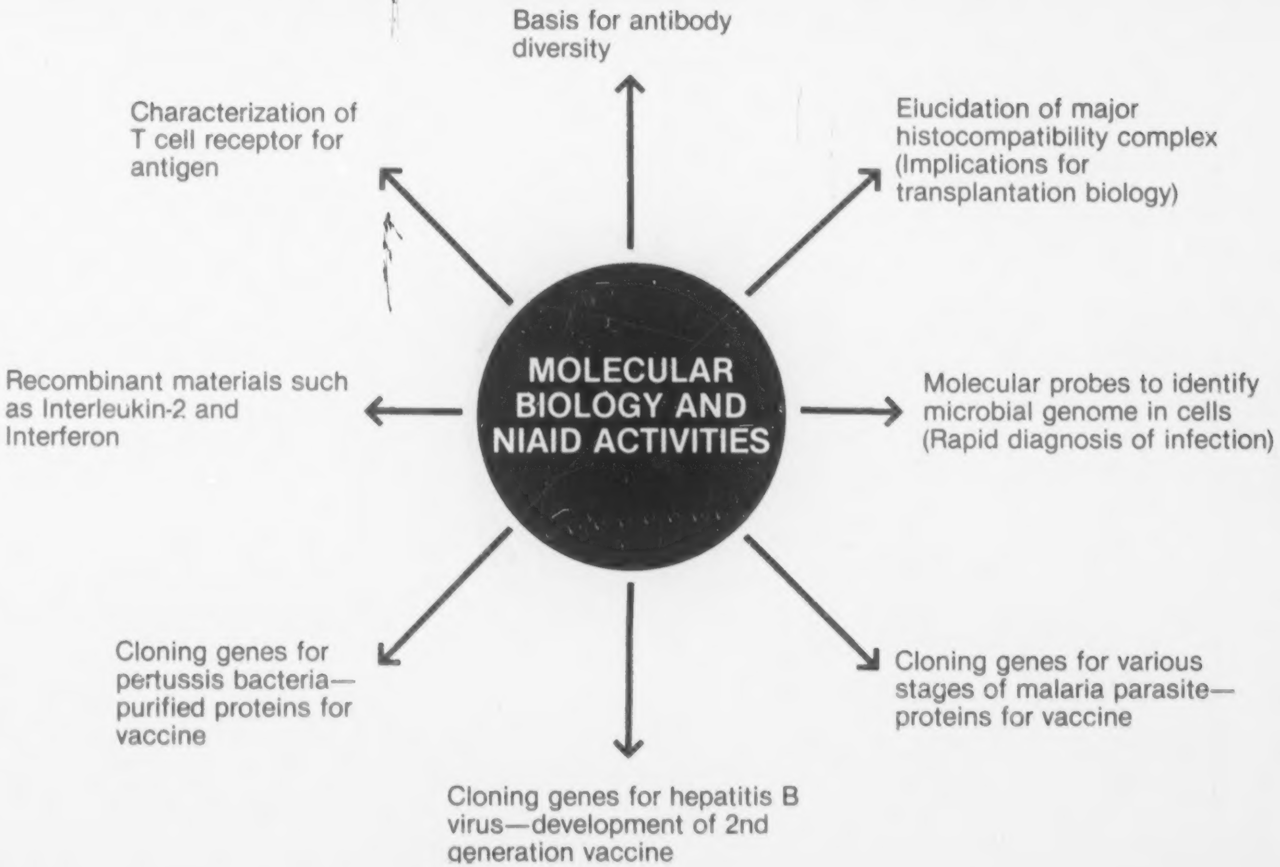
MOLECULAR BIOLOGY AND NIAID ACTIVITIES
Basis for antibody diversity
Elucidation of major histocompatibility complex (Implications for transplantation biology)
Molecular probes to identify microbial genome in cells (Rapid diagnosis of infection)
Cloning genes for various stages of malaria parasite—proteins for vaccine
Cloning genes for hepatitis B virus—development of 2nd generation vaccine
Cloning genes for pertussis bacteria—purified proteins for vaccine
Recombinant materials such as Interleukin-2 and Interferon
Characterization of T cell receptor for antigen

Figure 1.

PRINCIPLES OF GENE CLONING TO OBTAIN PURIFIED MATERIALS

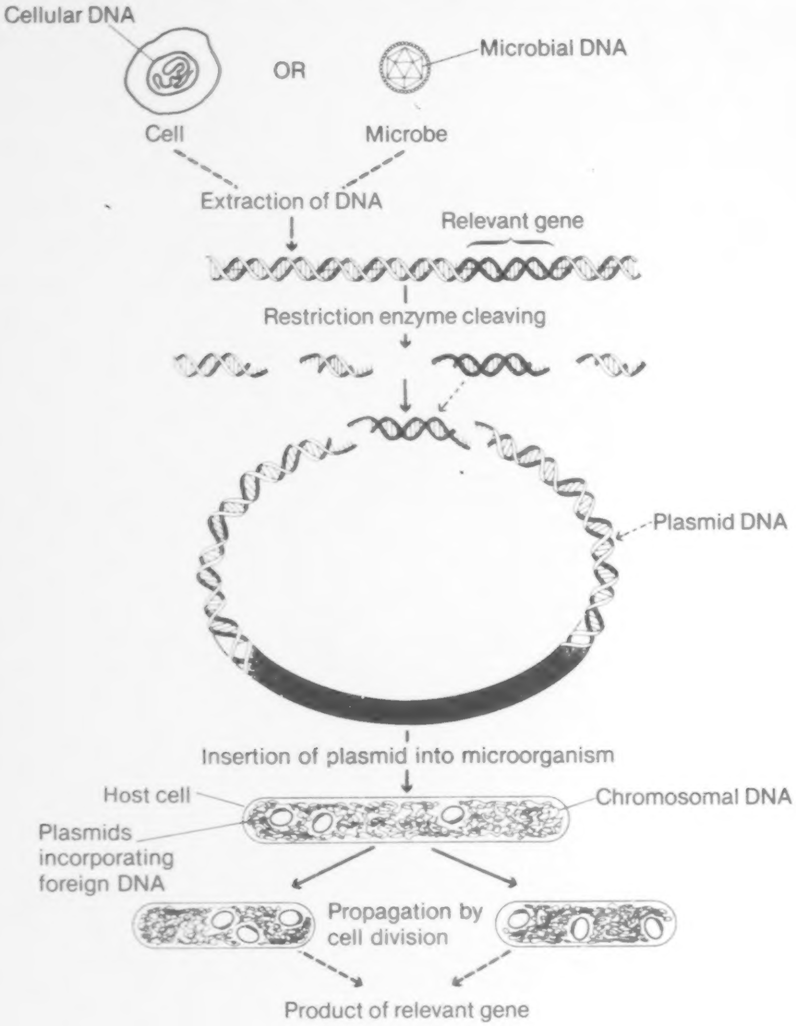
Cellular DNA
OR
Microbial DNA
Cell
Microbe
Extraction of DNA
Relevant gene
Restriction enzyme cleaving
Plasmid DNA
Insertion of plasmid into microorganism
Host cell
Chromosomal DNA
Plasmids incorporating foreign DNA
Propagation by cell division
Product of relevant gene

Figure 2.

Dr. **Fauci**. As shown in Figure 2, current technology has allowed us to take either a cell or a microbe, such as a virus, and be able to literally lay out the genes of the particular microbe or cell as if you were laying them out on the table. We can then identify the gene relevant for a particular function in which we are interested. I will give you a specific example of that in a moment.

We can also cut this gene out, a process called restriction enzyme cleaving, and then reinsert it into the DNA of a bacterium. The bacterium can then produce the product in unlimited quantities and in a highly purified form.

Mr. **Early**. Doctor, can I ask you one question?

Dr. **Fauci**. Of course.

Mr. **Early**. I am confused about the gene and the marker.

This morning, in a discussion of Huntington's disease you identified chromosome form. I thought that was the gene.

Dr. **Fauci**. Right.

Mr. **Early**. Is that the marker? What do you refer to as the marker, and the gene?

Dr. **Fauci**. In studies of Huntington's disease, scientists have not yet identified the gene causing the disease. But scientists have identified a nearby gene which is inherited along with the Huntington's gene; this is called a "marker." In the cases I am discussing, we actually have the gene we want. The gene codes for the production of a particular protein. In other words, it is the genetic information that tells the cell to make a particular protein.

Mr. **Early**. All right.

GENE CLONING FOR THE PRODUCTION OF HEPATITIS B VACCINE

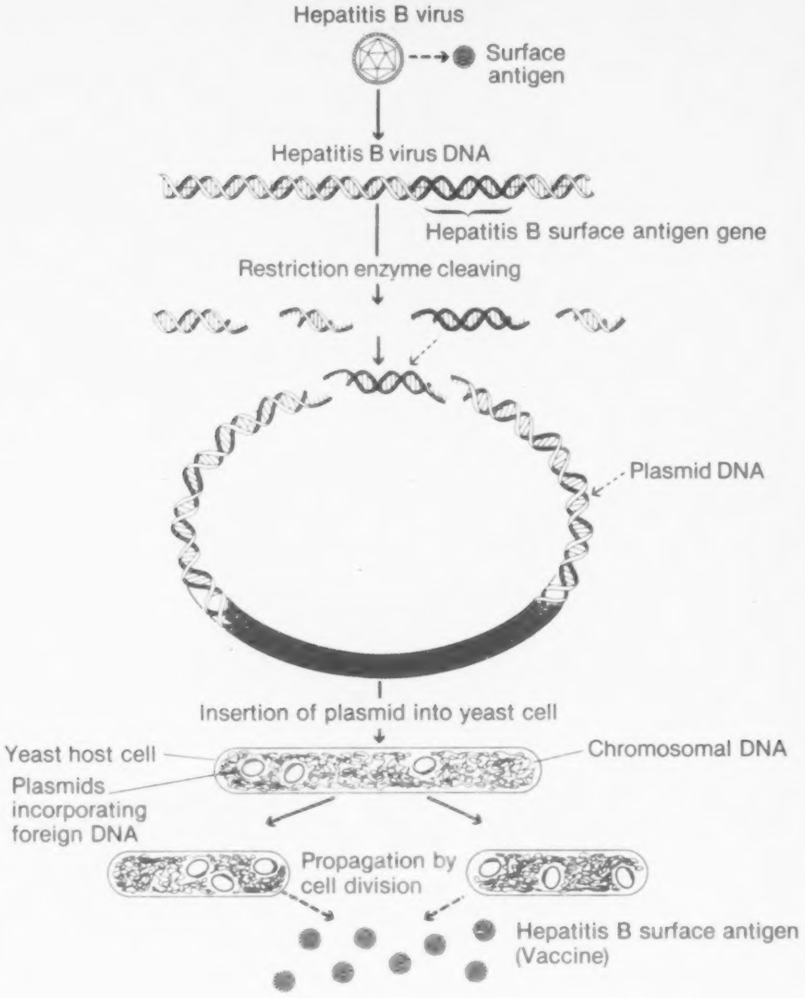
Hepatitis B virus
Surface antigen
Hepatitis B virus DNA
Hepatitis B surface antigen gene
Restriction enzyme cleaving
Plasmid DNA
Insertion of plasmid into yeast cell
Yeast host cell
Chromosomal DNA
Plasmids incorporating foreign DNA
Propagation by cell division
Hepatitis B surface antigen (Vaccine)

Figure 3.

Dr. Fauci. For example, we spoke about hepatitis B last year, how very expensive it was to develop a hepatitis B vaccine, because you had to take hundreds of gallons of plasma that contained the hepatitis B virus and purify it to get the vaccine. Now, as shown in Figure 3, using recombinant DNA technology, we know what we want is the surface antigen, which is the marker for this virus.

We then take the DNA and cut out the particular gene that codes for that antigen. We take that gene and insert it into this bacterial DNA, put it back into the bacterial cell, and grow the cell. Now that bacterium, or fungus, or whatever microbe is used, multiplies millions and millions of times

The cultured bacterium produces a number of proteins. One of the proteins is the hepatitis B surface antigen. So, instead of having to get hundreds of gallons of plasma you grow large numbers of bacteria which are acting like a factory now, and making surface antigens.

THE CAUSATIVE RETROVIRUS OF AIDS
(HTLV-III/LAV)

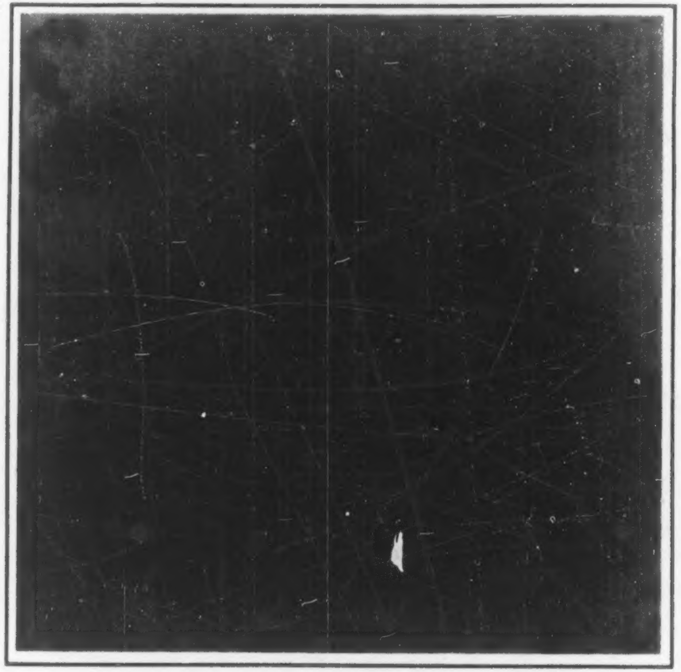

Figure 4.

Dr. **Fauci**. Let me move on very quickly. Figure 4 is one that I showed you last year in discussing the virus that is the cause of AIDS, HTLV-III/LAV. I said at the time that I was very certain that by now, a year later, we would be able to tell you a lot about this virus. Biomedical scientists, both at the NIH and outside, have been able to take the entire gene out of that virus and identify it, purify it, and clone it. We, therefore, know as much about this virus now as we know about virtually any virus.

HLTV-III/LAV GENOME (DNA)

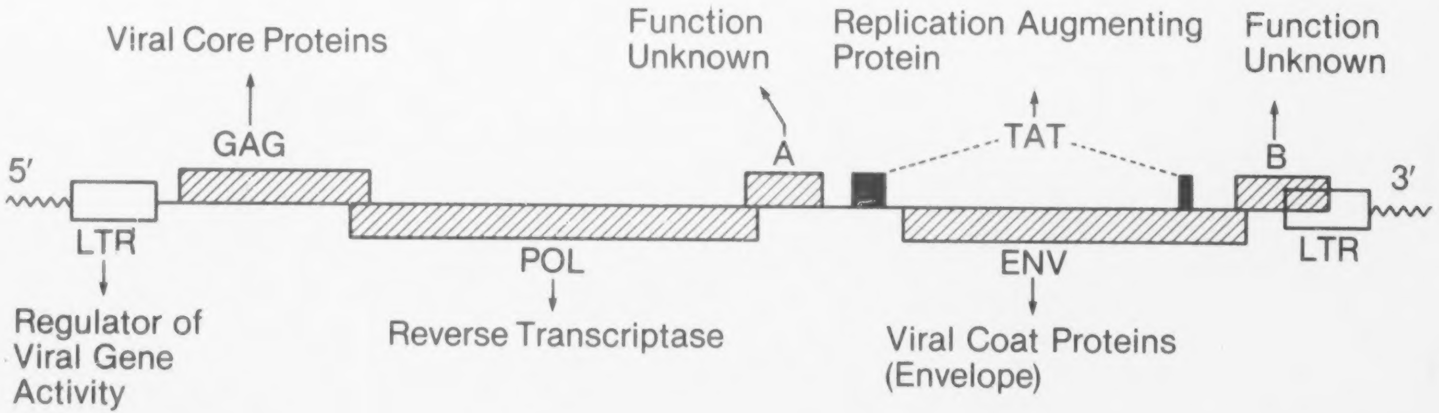
Viral Core Proteins
GAG
Function Unknown
A
Replication Augmenting Protein
TAT
Function Unknown
B
5′
3′
LTR
Regulator of Viral Gene Activity
POL
Reverse Transcriptase
ENV
Viral Coat Proteins (Envelope)
LTR

Figure 5.

Dr. FAUCI. These different colored coded segments on Figure 5 represent genes. They each code for a particular function of the virus. One of these is very important, and I think you probably have heard about it already. I refer to the envelope gene, which is responsible for coding for the proteins of the outer coat or envelope of that virus. This is important in immune response against the virus, and it is of utmost importance in developing a vaccine against the virus. We are now able to take that gene and insert it into bacteria and have the gene make unlimited quantities of this envelope, which is important to developing a vaccine. That is why we think a vaccine for AIDS in its earliest form is very likely imminent.

We have been asked a lot about what the NIH plan in general is for the treatment of AIDS. This is something that has been on the minds of a number of people.

STEPS IN DEVELOPMENT AND TESTING OF THERAPEUTIC AGENTS AGAINST AIDS RETROVIRUS

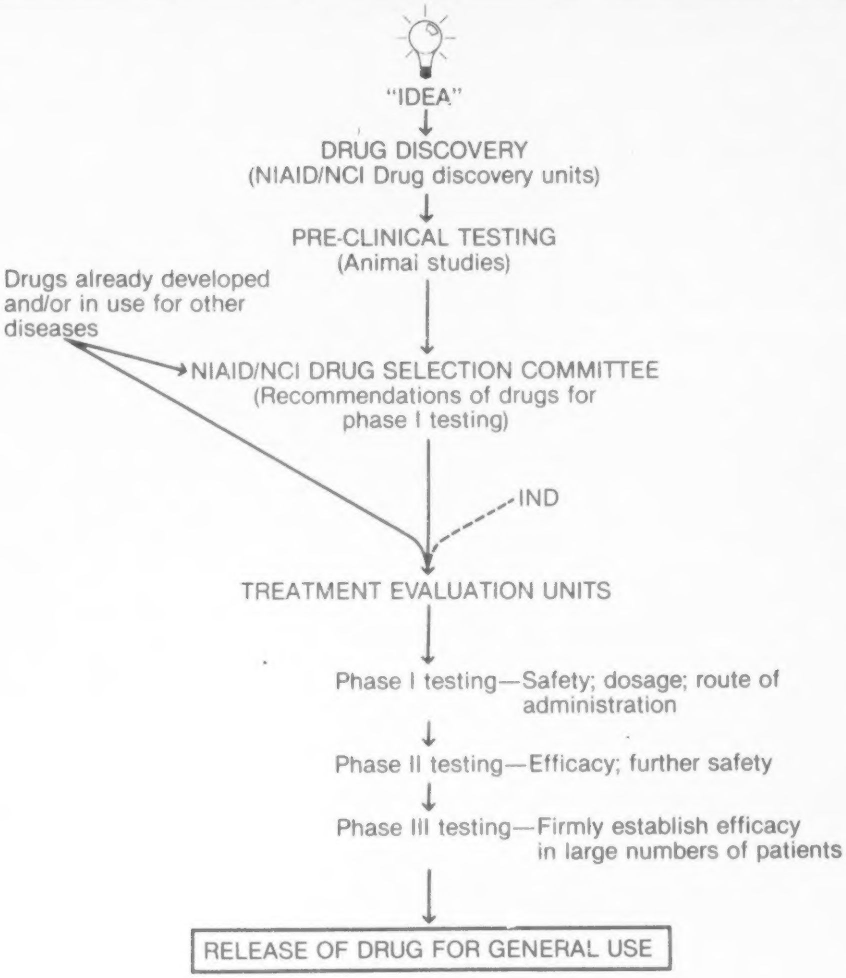
"IDEA"
DRUG DISCOVERY
(NIAID/NCI Drug discovery units)
PRE-CLINICAL TESTING
(Animal studies)
Drugs already developed and/or in use for other diseases
NIAID/NCI DRUG SELECTION COMMITTEE
(Recommendations of drugs for phase I testing)
IND
TREATMENT EVALUATION UNITS
Phase I testing—Safety; dosage; route of administration
Phase II testing—Efficacy; further safety
Phase III testing—Firmly establish efficacy in large numbers of patients
RELEASE OF DRUG FOR GENERAL USE

Figure 6.

Dr. FAUCI. We have a very well organized plan for the development of drugs for the treatment of AIDS, which is shown on Figure 6. It starts off with an idea for a particular drug. We will soon be funding cooperative National Drug Discovery Groups which will create and discover new drugs. The drugs will then go through preclinical testing in animals. We established an NIAID/NCI AIDS Drug Selection Committee, which makes recommendations concerning which of these drugs should ultimately go into preclinical and clinical testing.

We do not necessarily have to have a new drug. There are a number of drugs that have already been developed for other diseases. We can also channel them through the Drug Selection Committee, and then finally, through the AIDS Treatment Evaluation Units, which will be established sometime this summer for clinical testing. We are now in the process of evaluating the proposals for these contracts. In the Treatment Evaluation Units, these drugs will go through Phase I, Phase II, and then Phase III clinical testing; and hopefully, we will have drugs which can be released to the public.

ANTIVIRAL THERAPY IN AIDS

- Suramin
- Ribavirin
- Azidothymidine
- HPA-23
- Foscarnet

Figure 7.

Dr. FAUCI. Figure 7 shows a few of the drugs that have gone through the process that I have just outlined for you. You have probably heard of some of them. Suramin, ribavirin, HPA-23, Foscarnet, and azidothymidine, which was on the front page of the *Washington Post* this morning. There are many others that are coming into the hopper, and they will go through the same orderly procedure of testing that I outlined for you.

“THREE-PRONGED” APPROACH TO AIDS TREATMENT

- Treatment of opportunistic infections and Kaposi’s sarcoma
- Destruction and/or containment of AIDS virus by antiviral therapy
- Reconstitution or enhancement of immune response

Figure 8.

Dr. FAUCI. And finally, displayed on Figure 8, I show our approach to the treatment of AIDS, which we call our "three-pronged" approach. First is treatment of the opportunistic infections and Kaposi's sarcoma. These are the secondary complications of AIDS.

Then there is the destruction and/or containment of the AIDS virus by antiviral therapy, which I just mentioned to you in discussing the drugs. Finally, there is reconstitution or enhancement of the immune response. Our plan is to have a combined therapy to destroy the virus and, at the same time, to reconstitute the immune system. Hopefully, next year when I appear before you, we will be able to give you some of the results from these studies.

This concludes my opening remarks, Mr. Chairman. I will be happy to answer any questions.

[Statement follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of Allergy and Infectious Diseases

Over the years, research conducted and supported by the National Institute of Allergy and Infectious Diseases (NIAID) has made major contributions toward improving the health of our Nation and the world. More than half a billion people around the world suffer from diseases that are under intensive study by scientists supported by the NIAID. The backbone of our efforts lies in research at the basic cellular and molecular biological level. Indeed, it is basic scientific research in immunology, immunologic and infectious diseases that has laid the groundwork for the extraordinary development of knowledge about the acquired immunodeficiency syndrome (AIDS). Because of the public health crisis brought about by AIDS, we have been reminded in a most emphatic way that fundamental research allows us to respond quickly and with considerable expertise to emerging health problems.

The need for basic research holds true for other diseases as well, diseases that perhaps have attracted somewhat less attention than AIDS over the last year, but that cause illness and death for millions of people. Pertussis, or whooping cough, for example, is a disease that affects children in a most dramatic way, but due to successful childhood vaccination programs is one not often seen in this country. When I was before this Committee a year ago, we discussed the problems regarding the pertussis vaccine and our efforts to develop a purified vaccine without the toxic side effects that have been the cause of great concern. I am pleased to report to you today a new finding that will enable us to move more quickly toward the development of a safe and effective vaccine. Scientists in our intramural program have cloned and sequenced two of the five genes in the pertussis organism that are linked to production of the toxin causing the devastating effects of whooping cough.

As I described for you last year with regard to the malaria vaccine, the cloning and sequencing of genes that code for the proteins of pathogenic organisms are extremely important in the development of genetically engineered vaccines, comprised of purified products that induce protective immunity in the absence of toxic side effects. In addition, a number of acellular candidate pertussis vaccines, made by extracting appropriate antigens from the whole cell, are being developed and tested with NIAID support. This testing includes a large-scale efficacy trial in Sweden, where pertussis is epidemic and vaccination rates are low.

Although we have been successful in developing vaccines against a variety of microorganisms, particularly viruses, viruses as a group have long presented an obstacle to the clinician because they do not respond to the tools in our traditional armamentarium of pharmacologic therapies. The development of new antiviral agents gives us great hope for the treatment of the many serious illnesses caused by viruses, including AIDS.

One such drug is acyclovir, which, as I reported last year, is effective against a number of herpesviruses. It has been licensed for use in treating genital herpes. In studies recently completed, acyclovir was also demonstrated to be effective in treating herpes encephalitis and is undergoing testing for use in herpes zoster, or shingles. There is now evidence to suggest that acyclovir can prevent the devastating effects of neonatal herpes in newborn babies if given shortly after birth. Based on this promising evidence, clinical studies are proposed for 1987.

Antivirals have come under increasing scrutiny over the past several years due to our search for effective therapies for AIDS and the opportunistic infections that accompany it. Since my appearance before the Committee last year, the number of Americans known to be afflicted with AIDS has doubled. The 5-year projected mortality for persons with full-blown AIDS still approaches 100 percent. We estimate that more than one million Americans have already been infected with the virus and that approximately 10 percent of these will develop clinical AIDS within a 3-year period. With the identification of the causative virus, the delineation of the specific immune defect in AIDS, and the development of a blood test to protect the Nation's blood supply, we have now focused a great deal of attention on developing effective therapies for AIDS.

We have made great strides in developing and testing a variety of treatment strategies for both the underlying immune deficiency and for the array of devastating illnesses that actually cause the death of persons with AIDS. Phase I testing, which means determining the safest dosage and mode of administration, has been carried out for a number of antiviral agents, but it is still too early to tell if the drugs being tested will prove to be of clinical value.

One area in particular that we are vigorously pursuing is immune reconstitution. Once we have in hand a drug that can kill or inactivate the AIDS virus, we must be able to restore the ability of the immune system to function in order to defend the body against the opportunistic infections and cancers that prove so deadly to persons with AIDS. The reverse is true as well: if we are able to bolster the immune system, it will be of only temporary help as long as the virus continues to reproduce and invade other cells. Therefore, we have developed a strategy of using a combination of antiviral therapy and immune reconstitution. During the past year, we have studied three sets of identical twins, one of whom in each set has AIDS. The three healthy brothers have donated bone marrow and lymphocytes to their twins with AIDS. An antiviral agent, suramin, was administered to the AIDS patients to suppress or perhaps eliminate the virus. It is still too early to report results from these studies.

Another way to boost the immune system is through the use of interleukin-2 (IL-2), a protein naturally produced by normal T cells. Over the past two years, we have treated several patients with IL-2 and found that it can result in a partial reconstitution of the depleted lymphocyte count and a minor reduction in Kaposi's sarcoma tumors, indicating that it may play a potentially important role in immune reconstitution therapy.

The NIAID is collaborating with the National Cancer Institute in a comprehensive program for developing and evaluating treatments for AIDS, AIDS-Related Complex (ARC), and opportunistic infections. This program will encompass "Drug Discovery Groups" to discover and create candidate drugs for testing, the evaluation of potential drugs in the test tube, and the establishment of AIDS Treatment Evaluation Units for clinical testing of experimental therapies.

Development of an effective vaccine against the AIDS virus is, of course, of the greatest urgency. Studies at the molecular level have shown that viral isolates obtained from different geographic areas of the world differ substantially in the envelope glycoproteins, that is, the carbohydrate-protein compounds that are found on the outer coating of the virus. This variability will in all likelihood complicate our efforts to develop a protective vaccine. In addition, we need to know what constitutes protection in the case of HTLV-III/LAV. NIAID scientists have delineated the nature of the cellular and humoral immune response against the AIDS virus. These studies are critical components of the ongoing vaccine development strategy.

The NIAID is supporting natural history studies aimed at understanding how the disease is spread, and how it affects people in the high-risk groups over time. These studies may enable us to better understand such questions as what role various cofactors play in the development of disease in individuals infected with HTLV-III/LAV. We will also be expanding our international studies beyond Zaire in Central Africa to include populations in other areas of Africa, the Caribbean, and Asia.

AIDS is not going to disappear in the foreseeable future, and it is already a disease of monumental social and economic implications. The likelihood of future spread heterosexually into the general population will markedly compound the problem.

Thus, we are in the process of establishing an AIDS extramural management program to improve our planning and coordination of extramural research activities and to provide a central focus for our AIDS activities. This program will encompass all the things I have spoken of--therapeutics, vaccine development, clinical trials, pathogenesis, and epidemiology and international studies.

Tropical medicine and international health remain high priorities for the NIAID. One of the many benefits from research in tropical medicine has been the application of drugs such as suramin, which were originally used to treat tropical diseases, in treating AIDS and the opportunistic infections resulting from AIDS. African sleeping sickness, or trypanosomiasis, is a tropical disease caused by a parasite transmitted through the bite of the tsetse fly. Suramin has been used effectively to treat the disease before it affects the brain. Once the parasite has invaded the brain, however, suramin is not effective. Preliminary studies in Africa have shown that a drug called difluoromethylornithine (DFMO) when used in combination with suramin can cure virtually 100 percent of patients who have chronic central nervous system trypanosome infection. Even more recent work with a new form of DFMO has demonstrated that it results in lower toxicity than DFMO itself with equally promising results.

The study of immunology at the very basic level continues to provide insights and pathways to clinical advances in organ transplantation, autoimmune diseases, hypersensitivity diseases such as asthma, congenital immunodeficiency diseases, as well as the promising area of immunotherapy for immune-mediated diseases and cancer with agents such as interleukin-2 and the interferons.

This has been an exciting year for the NIAID in approaching and crossing the threshold between basic scientific discoveries and the application of these discoveries to the control of a wide range of diseases within the mission of the NIAID. This coming year will provide the opportunity to make further advances in the basic sciences of immunology and infectious diseases as well as to witness the fruition of the endeavors of previous years.

Mr. Chairman, the 1987 budget request for this Institute is $330,551,000. I will be happy to answer any questions.

FAUCI, DR. ANTHONY S.
Director, National Institute of Allergy and Infectious Diseases

December 24, 1940. Brooklyn, New York

Education:

College of the Holy Cross, 1962 - A.B.; Cornell University Medical College, 1966 - M.D.

Professional History:

1966-1967, Intern, Department of Medicine, New York Hospital-Cornell Medical Center. 1967-1968, Assistant Resident, Department of Medicine, New York Hospital-Cornell Medical Center. 1968-1970, Clinical Associate, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, Maryland. 1970-1971, Senior Staff Fellow, Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, Maryland. 1971-1972, Chief Resident, Department of Medicine, New York Hospital-Cornell Medical Center; Instructor in Medicine, Cornell Medical College. 1972-1974, Senior Investigator, Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, Maryland. 1972-present, Consultant in Infectious Diseases, The National Naval Medical Center, Bethesda, Maryland. 1974-1980, Head, Clinical Physiology Section, Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, Maryland. 1977-1984, Deputy Clinical Director, NIAID, NIH, Bethesda, Maryland. 1980-present, Chief, Laboratory of Immunoregulation, NIAID, NIH, Bethesda, Maryland. 1984-present, Clinical Professor, Department of Medicine, Division of Rheumatology, Immunology, and Allergy, Georgetown University School of Medicine, Washington, D.C. 1985-present, Clinical Professor, George Washington University School of Medicine and Health Sciences, Washington, D.C. 1984-present, Director, NIAID, NIH, Bethesda, Maryland.

Board Certification and Military Service:

American Board of Internal Medicine-June 21, 1972. American Board of Allergy and Immunology-March 1, 1974. American Board of Infectious Diseases-October 15, 1974. U.S. Public Health Service, July 1968-June 1970; July 1972-Present.

Professional Organizations:

American Federation for Clinical Research, American Association for the Advancement of Science, American Association of Immunologists, American Medical Association, Fellow of the American Academy of Allergy, Infectious Diseases Society of America, American Society for Clinical Investigation, Fellow of The American College of Physicians, Association of American Physicians, Collegium Internationale Allergologicum.

Offices Held:

Councillor, Eastern Section, American Federation for Clinical Research (AFCR), 1977. National Councillor, AFCR, 1978-1979. President, AFCR, 1980-1981.

Advisory Boards and Committees:

Chairman, Allergy and Immunology Committee, MKSAP V, American College of Physicians. Advisory Panel, The American Board of Medical Laboratory Immunology. Member, Committee on Clinical Immunology and Immunopathology, American Association of Immunologists, 1980-1985. Representative of American Association of Immunologists to the Examinations Committee of the American Board of Allergy and Immunology, 1981-present. Postgraduate Education Committee, American Academy of Allergy, 1979-1982. Member, NIAID Study Group on Immunology, 1980. Member, Section on Physiology in Clinical Science of the American Physiological Society, 1980-1984. Member, Subcommittee on the Classification of Vasculitis, American Rheumatism Association, 1980-present. Ad Hoc Committee, The National Foundation for Infectious Diseases, 1980-present. Subcommittee on Clinical Sciences, Publications Committee, American Physiological Society, 1980-1984. American Association of Immunologists, 1982-1985. Member, NIAID Working Group for AIDS, 1982-present. Member, American Federation for Clinical Research President's Public Policy Advisory Committee, 1983-present. Board of Directors, American Board of Allergy and Immunology, 1984-present. Participant in the USA - People's Republic of China Immunology Cooperative Agreement, August 10-22, 1983, Beijing and Shanghai, PRC. Member, Scientific Advisory Board, Medical Biology Institute, La Jolla, CA, 1983-1984. Participant in the USA-Japan Eye Immunology Advisory Conference, November 27 to December 1, 1983, Honolulu, HI. Member, External Advisory Committee, Multipurpose Arthritis Center, Duke University Medical Center, 1984-present. Member, Honorary Advisory Board, Italian-American Medical Association, 1984-present. Member, Peripatetic Club, 1984-present. Ex Officio Member, National Diabetes Advisory Board, 1984-present. Ex Officio Member, National Digestive Diseases Advisory Board, 1984-present. Chairman, Search Committee for Director, National Institute of Child Health and Human Development, 1985. Member, Department of Health and Human Services Task Force on Alzheimer's Diseases. The Albert Lasker Medical Research Award Jury, 1985-present. Deputy Ethics Counselor, Department of Health and Human Services, 1985-present. Member, Department of Health and Human Services Committee to Coordinate Environmental and Related Programs, 1985-present. Member, Scientific Organizing Committee, Joint Meeting of the Italian Society of Immunology and Immunopathology-National Institutes of Health on "Human Lymphocyte Activation," Florence, Italy, September 5-7, 1985. Member, United States Delegation to the United States-Japan Cooperative Medical Science Committee, 1985-present. Member, Scientific Seminar Subcommittee, National Institutes of Health Centennial Program, 1985-1987. Member, Advisory Board, Clinical Immunology Newsletter, 1986-1988. Member, Scientific Organizing Committee, International Conference on Lymphocyte Activation and Immune Regulation, Newport Beach, CA, February 28-March 2, 1986.

Editorial Boards:

Dr. Fauci has been or is on the Editorial Board of 26 sceintific journals in the field of immunology, allergy and infectious diseases. These include: The Journal of Clinical Investigation, The Journal of Immunology, Journal of Infectious Diseases, Journal of Clinical Immunology. Dr. Fauci is also the Editor of one of two major textbooks of medicine in the world, "Harrison's Principles of Internal Medicine."

Awards and Honors:

Alpha Omega Alpha. Kileen Prize for Excellence in Chemistry (College of the Holy Cross). John Metcalfe Polk Prize for General Efficiency (Cornell University Medical College). Alfred Mortitz Michaelis Prize for Efficiency in General Medicine (Cornell University Medical College). U. S. Public Health Service Meritorious Service Award, 1979. Arthur S. Flemming Award, 1979 Given to the 10 outstanding employees in the U. S. Federal Government. Squibb Award of the Infectious Diseases Society of America, 1983. U. S. Public Health Service Distinguished Service Medal, 1984. Food and Drug Administration Commissioner's Special Citation, 1984. 1985 Citation Classics (Current Contents) for article A. S. Fauci, D. C. Dale, and J. E. Balow: Glucocorticosteroid therapy: mechanisms of action and clinical considerations. Ann. Intern. Med 84: 304-315, 1976. Who's Who in America, 44th Edition. Who's Who in Science and Technology, 2nd Edition. 1985 Stanford University Center Survey of the American Rheumatism Association membership ranked the work of Dr. Anthony S. Fauci on the treatment of polyarteritis nodosa and Wegener's granulomatosis as one of the most important advances in patient management in rheumatology over the past 20 years. Professor of Medicine at a large number of major medical schools throughout the country.

Publications:

Dr. Fauci has authored over 500 scientific publications in the field of basic and clinical immunology and infectious diseases.

EPSTEIN-BARR VIRUS

Mr. **Early**. Leave the next to last chart up there, please.

Doctor, we are going to break the precedent that this Administration has set. The President thinks that foreign aid should be increased 12 percent, defense whatever percent, and NIH should be cut. Mr. Obey is the Chair of the Foreign Affairs Subcommittee, and we want him to save us a little of the money, not much, but a little of the money.

Mr. **O'Brien**. There is a Mr. Obey here. He is not talking about me. [Laughter.]

Mr. **Obey**. I thank the Chair.

You know it is true. In fact, I just left the floor where we are discussing the budget, and it seems as—I was there, I was talking. That is why you did not see me. [Laughter.]

But it really does seem absurd to me that we are being asked to increase grant military assistance—well, this Administration has increased grant military assistance by 800 percent since Ronald Reagan has become President. That is the give-away stuff that he used to squawk about before he took over in the White House, 800 percent.

This year alone, military assistance is up—the grant military assistance this year alone is up 30 percent. But that is beside the point.

Doctor, I would like to ask you some questions about something that I am really an ignoramus about.

Epstein-Barr virus, tell me about it. What do we know about it? What causes it? How do you get it? Is it easily transmissible? What is the prognosis for people who have it?

Dr. **Fauci**. Epstein-Barr virus is a virus that has a particular propensity to attack a cell in the immune system, called a B cell.

It is a very interesting virus. Virtually everyone in this room has been exposed to and very likely infected with Epstein-Barr virus at one time in their lives. Most of the time you get an asymptomatic infection which means that you get infected but you either do not get sick at all or you have very few symptoms.

Another subset of individuals get classic infectious mononucleosis caused by the Epstein-Barr virus.

Still another subset of individuals do not have the immune mechanism to destroy the virus, and go on to develop neoplasms or B cell lymphomas.

Another smaller group of individuals have a chronic Epstein-Barr virus syndrome often referred to as chronic mononucleosis, a syndrome that might last from one to two years. It is characterized by some fever, some malaise, and just not feeling well.

Really, the virus is extraordinary because it can do everything from giving you a totally asymptomatic infection to killing you with a neoplastic process.

Mr. **Obey**. For a person who falls into that latter category, not just mono, who does not get off scot free, what is the percentage of people who died from it, who proceed to that third stage?

Dr. **Fauci**. That is literally a fraction of a fraction of 1 percent.

Mr. **Obey**. A fraction of 1 percent?

Dr. **Fauci**. A fraction of a fraction of 1 percent.

RESEARCH ON EPSTEIN-BARR VIRUS

Mr. **Obey**. What kind of research have you been doing on it in the past?

Dr. **Fauci**. We have been doing a considerable amount of research, Mr. Obey. In our Institute, we are very interested in the interaction between viruses and cells of the immune system. The target of this virus is a cell of the immune system. We have conducted a lot of research in that area.

We have cloned the total genome of this virus. Just as I showed you earlier on a chart where we did that with the hepatitis B virus and the HTLV-III AIDS virus, we have done the same thing with the Epstein-Barr virus.

We have also been able to identify antigens that the virus codes for when it enters a cell—in other words, how it changes a cell. Also, we have been able to develop monoclonal antibodies against a variety of the components of this virus. We have actually gotten down to the molecular level in the study of this virus.

Unfortunately, like many viral illnesses, there is not a good treatment for it, one through which you can completely wipe out the virus. It is one of those viruses that you can walk around with and be completely well, but you still would be infected with it. It is a herpesvirus, similar to the herpes simplex that causes cold sores.

FUNDING FOR EPSTEIN-BARR VIRUS

Mr. **Obey**. Are any new studies being considered for funding next year?

Dr. **Fauci**. The major mechanism of funding for this type of research is the investigator-initiated research project grant. We have a number of grant applications that are in the process of being evaluated by study sections, and others that have been funded in previous years.

Mr. **Obey**. Do you have meritorious research proposals which have already been peer reviewed that you are unable to fund under budget constraints in this area?

Dr. **Fauci**. We are still in the process of getting the final priority scores on grant applications.

Mr. **Obey**. So you cannot tell us what you—what is your payline for R-01s this year?

Dr. **Fauci**. Right now it is 150.

Mr. **Obey**. And you do not know where those cluster?

Dr. **Fauci**. Well, what will happen, Mr. Obey, is that——

Mr. **Obey**. I am talking about the year we are in now.

Dr. **Fauci**. Yes, the year we are in now.

I do not have at my fingertips, the priority scores for the Epstein-Barr virus grant applications. We could make that information available to you.

The final decision on funding will be made after the May meeting of our National Advisory Council because the Council will review the grants in May. At that time we will have a better idea as to where in the lineup of priorities these grants will fall by priority score.

Mr. **Obey**. How many R-01s last year involved studies that were related to Epstein-Barr?

Dr. **Fauci**. I do not think I have that information. I could supply that for you for the record.

Mr. **Obey**. Any idea? Any rough guesses?

Dr. **Fauci**. Yes. Actually we do have that information.

Last year, in FY 1985, there were 19.

Mr. **Obey**. Any guess this year what they are going to be? What the number is going to be?

Dr. **Fauci**. Usually from one year to another in an area such as this, which has a stable level of interest, there is not much change. Therefore, I would predict that it would be somewhere around 19 or 20.

Mr. **Obey**. I have got a number of other questions on that and two other problems which I will submit for the record.

I thank the Chairman.

Mr. **Early**. Mr. Hoyer.

AIDS—NEW RESEARCH

Mr. **Hoyer**. Thank you very much, Mr. Chairman. I thank Mr. Conte for yielding. I have to go to the House floor.

First of all, Doctor, what new AIDS research efforts will you initiate in fiscal year 1987?

Dr. **Fauci**. In fiscal year 1987, we will not initiate any new efforts. We will continue ongoing activities.

Mr. **Hoyer**. You are going to continue all the efforts?

Dr. **Fauci**. Right.

AIDS—FUNDING

Mr. **Hoyer**. If you had some additional funds, would it be appropriate to initiate new efforts?

Dr. **Fauci**. The situation in FY 1987 for AIDS research is that funds have not been allocated to the Institute. The funds for AIDS are going into a single account in the Office of the Assistant Secretary for Health. Thus, it is not a question of new funds being made available to us.

Mr. **Hoyer**. Do you have any ideas at this point how those funds will relate to your utilization of them? How is that going to work or do you know?

Dr. **Wyngaarden**. Maybe I could try that, Mr. Hoyer.

I inquired about that and have been assured that the commitments made during FY 1985 and FY 1986 that carry forward into FY 1987 will be met by transfer of the appropriate funds from OASH to NIH. Beyond that, I do not think there has been any decision about the uncommitted funds as yet. Whether we can make any——

Mr. **Hoyer**. What are the alternatives to that as opposed to giving them back to NIH and allowing those people who have been doing the work to continue the work and utilize those funds?

Dr. **Wyngaarden**. At the request level in FY 1986, we will generate commitments for FY 1987 that would probably consume most, maybe not quite all, but most of our original request for FY 1987 which was $143 million for NIH AIDS research. We will have a base of about $123 million, I believe, in 1986. With the normal increase in costs of the projects, we do not know what the window will be.

The question that needs to be addressed by the Assistant Secretary concerning AIDS funds that are available over and above existing commitments is whether those should go into research at the NIH, or whether there is something in the control area at CDC, for example, that may have a higher priority. And that, I do not believe, has been addressed yet.

Mr. HOYER. Who should address that question now?

Dr. WYNGAARDEN. Dr. MacDonald would be the person to speak to that at the moment.

Mr. HOYER. Dr. Fauci, what will be the impact of having AIDS funds for fiscal '87 in the Office of the Assistant Secretary for Health, as far as you are concerned?

Is this going to impede your work in any way?

Dr. FAUCI. Well, we would have to assume the reimbursement of funds from OASH that we would need to support our continuing activities and our commitments.

With regard to how that would affect us, I would have to presume that we will be getting that allocation and make plans with that in mind. There might be some anxiety among the individuals to whom we have made commitments; for example, those with ongoing commitments in research activities because we do not have the money right now. We have been assured that we will get the money, but we do not have the money now.

Mr. HOYER. And do you believe that there is no doubt that the money is going to come back to the extent of the '86 commitments? Dr. Wyngaarden?

Dr. WYNGAARDEN. Yes, I am reasonably sure of that.

Do you want to add to that, Mr. Williams?

Mr. WILLIAMS. No. I think that is probably right.

AIDS—FTES

Mr. HOYER. Dr. Fauci, you received considerable additional funding in fiscal year '86.

The question is, did you receive the FTEs, the slots, the people to carry out those functions which you would have been expected to undertake because of the additional funding?

Dr. FAUCI. We received 11 FTEs for AIDS research. As you know, we are in a situation in which FTEs are being decreased at the NIH.

Mr. HOYER. How many would you have needed? How many did you project you would need? Let me put it that way.

Did you have a request for FTEs that accompanied your request for funds?

Dr. FAUCI. Well, in 1986, associated with the new initiatives, the request was for 26.

Mr. HOYER. So, although money was committed, you got less than half of the FTEs you requested?

Dr. **Fauci**. The 11 we got were requested in the first 1986 budget amendment, and then for the new initiatives in 1986, we requested another 26.

Mr. **Hoyer**. So, actually, you got what must have been a third of what you would have needed because the request would have actually been for 37 and you got 11?

Dr. **Fauci**. Right.

Mr. **Hoyer**. Now, having been shortchanged that badly, can you effectively carry out your mission, the research outreach that we wanted in the Congress and demonstrated by the additional funds? Who made that decision, Jim Miller or David Stockman, do you know? Did OMB make that decision or did the Department make that decision?

Dr. **Fauci**. I do not know, Mr. Hoyer.

Mr. **Hoyer**. Well, let us go back to the original question.

Is that not undercutting our—it seems to me if we give you a lot of money to carry out projects, it is nice to have the money there, but if you do not have the people to implement it, it seems that the money will get caught in the pipeline and somehow the effort is not going to be effectively carried out.

Dr. **Fauci**. Well, what we have done in our Institute is to absorb the FTEs from other activities. We have now 57 FTEs designated for AIDS research, and all but 11 have been absorbed from other programs within the Institute.

Mr. **Hoyer**. So, notwithstanding the fact that the Congress, both Senate and House, thought this was a new effort, and added substantial sums, in effect what we have done is we are robbing some other very important projects, I presume, in order to carry out the AIDS research.

You do not have to adopt my adjectives. [Laughter.]

Dr. **Fauci**. Effectively speaking, we have had to take from other programs, yes.

AIDS—HETEROSEXUAL TRANSMISSION

Mr. **Hoyer**. What is the evidence that heterosexual transmission of the AIDS virus is occurring in the United States, particularly from females to males?

Dr. **Fauci**. Well, the evidence we have now in the United States comes from studies of Armed Forces personnel who have no other risks. They are not male homosexuals and are not intravenous drug abusers. Their only apparent risk is heterosexual promiscuity, including relationships with prostitutes. We know, from a number of studies, that many prostitutes are antibody positive and that, in fact, one can isolate the AIDS virus, for example, from vaginal secretions.

Clearly there are prostitutes who have the virus and have it in a way that could be transmitted heterosexually.

I think if you combine that with the information that we have from outside the United States, particularly from Central Africa where it is quite clear that there is heterosexual transmission from man to woman and from woman to man, there is, I think, no question that heterosexual transmission is occurring. But, unfortunately, as with the male homosexual population, we will not see the full impact of heterosexual transmission until a few years from now because the incubation period is up to 5 years, if not longer.

We are concerned about a potential upswing now in heterosexual by transmitted cases.

ALLERGIC SUBSTANCES IN THE WORKPLACE

Mr. **Hoyer**. I have a couple of other questions, Dr. Fauci. I will submit them for the record.

But one last one. I have heard that significant numbers of individuals are allergic to animals and substances in the workplaces.

What research approaches are being taken to depress these kinds of allergies?

Dr. **Fauci**. Formerly, as you may know, Mr. Hoyer, it was suggested that if an individual was allergic to a substance in his workplace, he just changed his job. Obviously, that is not feasible for people, both from an economic standpoint and from a personal standpoint. There are ongoing studies funded by our Institute evaluating immunotherapy to try to desensitize individuals to the particular antigen in the workplace to which they are sensitive.

In addition, there is another study to try to identify markers that would predict which individuals would be sensitive to substances within a given workplace—to try to screen them beforehand—to avoid having that person enter a job only to find out that he cannot function in that job. I think the latter approach would also be quite helpful.

Mr. **Hoyer**. That will have much broader implications as well, will it not?

Dr. **Fauci**. Yes, it will.

Mr. **Hoyer**. Mr. Chairman, I thank you very much for allowing me to go out of turn, and I want to thank you again, Mr. Conte, for yielding to me.

Thank you, Dr. Fauci.

Mr. **Early**. Mr. Conte.

AIDS—FUNDING AND COORDINATION AT OASH

Mr. **Conte**. Thank you, Mr. Chairman.

Dr. Fauci, I am really pleased to see you back here before the Subcommittee again. It has been an incredibly fast-paced year for you as Director of the Institute. The country is asking a lot of you and your colleagues, but we have confidence in you. And you do a good job.

Insofar as we discuss the NIH AIDS research budget, and how that budget will be administered under the structure of an AIDS Coordinator located in the Office of the Assistant Secretary for Health, I get the sense that it is not yet clear as to who will make the decisions about how the NIH AIDS research money will be spent. Would it make sense for that AIDS Coordinator to take over what has been essentially an NIH function for receiving proposals, reviewing them, and deciding which has merit to be funded; or do you think that it would make more sense to have NIH continue to carry on with its time-tested role of deciding how best to use research dollars, within whatever overall coordinated policy and strategy that may be worked out in conjunction with the Office of the AIDS Coordinator?

That was a long question.

Dr. **Fauci**. Well, the decisions about the research that have been made up to this point at NIH, by me and my colleagues, the other Institute Directors and Program Directors, will stay intact. The decisions about the research will stay at the NIH level. I do not think anyone foresees decisions being made at the Office of the Assistant Secretary level from the standpoint of the direction that the research should take.

We will coordinate overall AIDS efforts there. In fact, this coordination has been going on already. We have an NIH AIDS Executive Committee, co-chaired by Dr. Wyngaarden and me, which coordinates NIH AIDS activities. Both of us are members of the Public Health Service AIDS Executive Task Force, which coordinates NIH activities, with those of CDC, ADAMHA, FDA and the rest of the PHS.

From a scientific basis, I do not anticipate any difference. The difference that you are hearing about is that before, the money was appropriated to the NIH, and now the money will be appropriated to the Office of the Assistant Secretary for Health.

The coordination has been going on and will continue to go on. I do not foresee there being any value judgments made about the research. The only difference will be whether the money will come for the research.

Mr. **Conte**. Do you think that is a good idea for OASH to give out the money? [Laughter.]

Dr. **Fauci**. Well, that is a very difficult question, Mr. Conte.

Mr. **Conte**. How about anyone other than NIH.

Dr. **Fauci**. I think that I would probably feel more comfortable if I knew that all the parties understood all the implications.

Mr. **Conte**. Do you feel a lot of grief about the situation? [Laughter.]

Dr. **Fauci**. I guess my feeling is that you do not have the money until you have the money. I think there may be some concern about that.

Although we have assurances of getting the money, the issue is that we are dealing with a situation in which money that has already been committed for ongoing extramural activities, intramural activities, FTE salaries and things like that, will not be in the NIH any more. I think that is the concern of some individuals.

Mr. **Conte**. So what will happen. The money will go to the Assistant Secretary for Health's office and that person can distribute it to the NIH, is that right?

Dr. **Fauci**. Yes. The money will go directly to the Office of the Assistant Secretary. So, in essence, there will be no AIDS money——

Mr. **Conte**. And then distributed to NIH?

Dr. **Fauci**. To NIH and to the other agencies, yes.

Mr. **Conte**. Is that all right, Doctor?

Dr. **Wyngaarden**. That is the plan. [Laughter.]

Mr. **Conte**. I feel I am not getting a straight answer. [Laughter.]

Dr. **Wyngaarden**. That is the plan.

Mr. **Conte**. I see. That is the plan.

Do you like the plan?

Dr. **Wyngaarden**. I have to say that I think it will work. We did appeal it without success.

Mr. **Conte**. Is there something we can do to ensure that NIH will continue to have fiscal latitude?

Dr. **Fauci**. That fiscal latitude might relate to the discussion we have just had.

Mr. **Conte**. Yes.

Dr. **Wyngaarden**. If I may interrupt, Mr. Conte. I do not think that putting the money in one place should affect the ability to devote resources, or to increase or shift resources from one to another at any given instance. To the extent that additional resources may be required, there is a decision making process now that requires the involvement of the Assistant Secretary and other elements of the Department.

If that situation would remain under this circumstance, the same elements in the decision making process would be involved. So I do not see that the mechanism itself or the form and location of the money really changes that process particularly.

Putting the money in one place does not necessarily change the method of operation in real terms. The work will still be done in the same locations that it is done now. It is just a way of keeping track of the total activity and making sure that people are aware of what is going on.

Mr. **Conte**. Well when we wrote that in the report, I certainly never had that intent. My intent was that we would have a coordinator and he would coordinate the AIDS research programs, the education and prevention work, and whatever else we've got going. But I always thought that the NIH money was going to go directly to the Institutes and not to the Assistant Secretary for Health. We may have to do a little more writing because that was never the intent of this Committee, I do not think.

Dr. **Wyngaarden**. I agree that the proposal now in the budget is a little bit different than had been discussed by your Committee.

AIDS—ANTIVIRAL DRUGS

Mr. **Conte**. Doctor, I caught a look at the article on the front page today talking about the rapid progress in experimental drugs to help the body fight off the AIDS virus. It looked pretty promising, but so have a lot of other things that I have read in the newspaper, only to be discouraged later.

What are your thoughts on some of these experimental drugs, particularly this AZT that is talked about in this large long article in the *Post*?

Dr. **Fauci**. Mr. Conte, we should all be cautious that when we read things like that, we understand that the entire research process is building up little blocks of knowledge and little blocks of progress in our fight against the AIDS virus. That is not a breakthrough. It is an interesting and potentially important new advance that needs testing.

Last year, for example, you may have heard about suramin being a very interesting and important drug. Well, we warned people that this would require further extended testing. In fact, we did that testing on a larger number of patients. As it is turning out, not only has the early enthusiasm that this drug would be the answer been dampened, but the drug has been shown to be quite toxic. And if we did not go through the well-tried and tested mechanisms to nail down the safety and effectiveness, we might have been in a situation of claiming to have something that we did not really have.

Although I have optimism about these little building block advances, I do not think we can say that the ball game is even close to being over on this virus.

Thus, that is a nice interesting article, but that is all it is.

Mr. Conte. In reading that article, you would think that this was a cure.

Dr. Fauci. Unfortunately, that is the way things come across sometimes when you read them in the lay press.

Mr. Conte. How many experimental drugs are there in the testing phase now?

Dr. Fauci. We now are considering for testing 29 new drugs out of several hundred that have been submitted to the AIDS Drug Selection Committee. The five that I listed on Figure 7 are ones that are currently between Phase I and Phase II testing. Those are suramin, HPA-23, Foscarnet, azidothymidine, and ribavirin. Those five are now being very actively tested in different medical centers throughout the country.

Mr. Conte. Do you have any idea how many AIDS victims are being involved in these trials?

Dr. Fauci. Yes. Once the AIDS Treatment Evaluation Units are operational this summer, we hope to be able to evaluate drugs in up to 2,000 people per year. That will be a substantial number, and we should get some good information out of those studies.

Mr. Conte. These drugs that are being tested are aimed at boosting the body's immune system, which is essentially destroyed by the AIDS virus. How far along are we in addressing the other half of the problem, that is, getting the body to actually kill off the virus itself?

Dr. Fauci. The drugs that I just mentioned are, in fact, aimed at killing the virus.

The third component of our three-pronged attack is to enhance the body's immune system. We are attempting to do that by bone marrow transplantation, or by infusing substances such as interleukin-2 or the interferons. Very active studies are going on in this area. What we hope to do is to combine the antiviral approach that kills the virus or inhibits the growth of the virus, together with the use of immune enhancers to gear up the body's own defense mechanisms to overcome the virus. We feel no drug alone is going to cure the disease. We are going to have to use a combination of an antiviral drug and these immune enhancers.

Mr. Conte. Well, I guess I have used my time, Mr. Chairman. I will return, Doctor.

AIDS—FUNDING AT OASH

Mr. **Early**. Since the Chair hasn't used any time, I want to continue briefly on the subject Mr. Conte was talking about.

That chart that you presented to the Committee is exactly what we are looking for. We asked for an idea, we asked for discovery, we asked for a vaccine, and we asked for education. That's what you are doing. That's what I thought you were going to do.

Not being facetious. The third step, Dr. Fauci, another committee? Why wouldn't you, Dr. DeVita, and Dr. Wyngaarden—even though Dr. Wyngaarden isn't an Italian—make the decisions and skip that new committee?

I mean, we've got to get there as quickly as we can. You know, we don't need more people making these decisions. You'd probably take a lot of heat, but what do you need that additional committee for?

Dr. **Fauci**. I might be the former Director of the Institute.

Mr. **Early**. Yes, for sure. You don't have to answer. I don't think you need it. But you certainly outlined the strategy for the development and testing of drugs which the Committee was looking for.

Doctor, all the funding to support the people working in your intramural program is over there, isn't it?

Dr. **Fauci**. Yes. The money for our intramural program's work on AIDS would now be in the Office of the Assistant Secretary for Health.

AIDS—REDIRECTION OF STAFF

Mr. **Early**. Were these people hired specifically for AIDS research, or were they shifted from other areas?

Dr. **Fauci**. 46 out of 57 were shifted from other areas.

AIDS—REDIRECTION OF FUNDING

Mr. **Early**. How about the extramural money, shifted over the last 3 or 4 years, from the non-AIDS areas?

Dr. **Fauci**. Yes. There has been a significant amount. We calculated that about $20 million was redirected from other areas into AIDS research in our Institute.

AIDS—COORDINATION OF RESEARCH

Mr. **Early**. Dr. Fauci, if we just go on the assumption that everything is going to be worked out, I don't want to go on. You know, 3 years even 2 years ago, we had money, and it ended up down at CDC, which is statistics. We don't need that. We need the discovery, a vaccine and education. I'm not going to support this approach.

I really think what is frustrating me the most is that the directors' independence and autonomy, is being taken away.

Tell me this, Doctor, we wanted a collaborative effort. Mr. Conte wanted one person in charge so we would know what was happening on AIDS. I understand DOD has quite a bit of money for AIDS research. Is that true?

Dr. **Fauci**. They do, sir.

Mr. **Early**. Do they contact you at all?

Dr. FAUCI. Yes, they do.

Mr. EARLY. Do we have any overlapping research?

Dr. FAUCI. We are serving in an advisory capacity to them to avoid overlap so that they might more appropriately use their funds. I have been contacted by and have met with officials from the DOD, particularly individuals at the Walter Reed Army Medical Center. My staff in our AIDS program have also met with them, and we hope to continue our coordination so that we will make the best use of the money.

Mr. EARLY. Doctor, do you know how much money they have?

Dr. FAUCI. Yes, I do, sir.

Mr. EARLY. How much?

Dr. FAUCI. They have $40 million for basic research, and $42 million for clinical care.

Mr. EARLY. And we've got you at NIAID and NCI overseeing. You people are supposed to be the experts. There's got to be someone that the AIDS information comes to. That was the third part we talked about, education. What really bothers everyone on this Committee, as it bothers everyone, is that a 12 year old hemophiliac cannot go to school.

You know, someone is supposed to be going out and saying whether that boy can go to school.

If we have a little over here and a little over there, we are spreading it too thin. We are not achieving what the Committee's intentions were. OMB has got us going in the opposite direction, as far as I am concerned.

Do you think your autonomy has been affected at all?

Dr. FAUCI. In this area?

Mr. EARLY. Yes. Specifically in this area.

Dr. FAUCI. Well——

Mr. EARLY. What if the Assistant Secretary decided not to give the money back to you?

Dr. FAUCI. Then my autonomy would be very severely affected.

Mr. EARLY. It would not be affected, it would be destroyed.

You would have no money.

Dr. FAUCI. That is correct.

Mr. EARLY. We are going to get much more specific on that. From the beginning, we set three goals: discovery, a vaccine, and education. And the other day someone came in here and said it is going to take us 3 years. We cannot afford 3 years, Doctor.

In your comments you said we might get to a vaccine fairly quickly. I want to get into that, I am going to yield to you, Mr. O'Brien.

Mr. O'BRIEN. Thank you, Mr. Early.

Well, doctor, it is good to have you back. It is my recollection that years ago, in the play, *Camelot,* Arthur is musing and he keeps thinking about his constituents, if you will, and he comments that they are all a bundle of drops, like drops of water in a sea. And that all are about the same but a handful sparkle. And you are one of the handful.

Dr. FAUCI. Thank you very much, Mr. O'Brien.

AIDS—REDIRECTION OF RESOURCES

Mr. O'Brien. With respect to your autonomy and authority in the handling of your Institute, it seemed to me that faced with the responsibility of dealing with the AIDS problem and being cut back to 11 from 37, you did manage to shift gears within the Institute. I think that was commendable. And I do think that you got through to what you were supposed to do from our mandate as best as you could. I had the impression that probably lower priority research lines may have suffered. But as near as I can determine from your testimony, I am not aware that you did not make do pretty well with what we gave you and with your responsibility to live under the restraints of the governmental system.

Is that about right?

Dr. Fauci. We had to make some difficult choices, Mr. O'Brien, because we felt the necessity to move quickly on the AIDS problem at the outset and even now. We had to constantly reevaluate our efforts in other areas and try as best as possible to keep the highest priority in those other areas going, while at the same time, we took resources from those areas to put into AIDS.

And they were difficult choices. It was very tough.

Mr. O'Brien. If you were reviewing what you have done over the year, had you been given the 37, and had you been unconstrained in any fashion, would you have behaved any different than you did, and would your results have been any different, in the three areas?

Dr. Fauci. Well, the activities would have been different. For example, in our hepatitis and slow virus disease program, and a variety of other programs, such as basic molecular biology, we had to put some activities on hold. Had we had additional resources they could have gone up to full throttle.

Mr. O'Brien. But that would be something in the field of shortcomings in the program.

Dr. Fauci. We did what we had to do.

Mr. O'Brien. Several years ago, I think it was the estimate that allergic and infectious disease simply dealt with the quality of life. We found to our surprise that allergic and infectious disease really was number five in the leading causes of death among the population in the United States, is that true?

Dr. Fauci. That is quite correct. They are still a major cause of death in this country, at all age levels.

Mr. O'Brien. When we talk about adjusting staffing levels to where we think that they should rest or should rise, it seems to me that our point in this Committee has been made very clear. And we rely on people like yourself and Dr. Wyngaarden and your counterparts, as well as the head of the department to make things work, with what we give you. We seem to be curbed by outside personnel who do not have expertise or clarity regarding the problems that you face. I guess I am trying to make a closing argument. We will continue to try to do that. And you keep trying as well.

Dr. Fauci. Thank you, we will.

Mr. Early. Doctor, if you can be brief in your answers and expand on them for the record, that would be fine.

Dr. Fauci. I will.

AIDS—FUNDING

Mr. **Early**. How much is presently in NIH for 1986 and 1987 for AIDS research?

Dr. **Fauci**. In 1986, with the reimbursement from the Office of the Director of $35,527,000, it will be $61,430,000.

Mr. **Early**. And how would that compare with 1985?

Dr. **Fauci**. In 1985 we obligated $23,273,000.

Mr. **Early**. Will you tell us what is in each Institute?

Dr. **Fauci**. In each Institute?

Mr. **Early**. Yes.

Dr. **Fauci**. Well, I have just given you the figures for my own Institute.

Mr. **Early**. Dr. Wyngaarden, will you supply for the record the amount for each Institute?

Dr. **Wyngaarden**. Yes, fine.

[The information follows:]

CUMULATIVE AIDS FUNDING SUMMARY, NATIONAL INSTITUTES OF HEALTH 1985-87

[Dollars in thousands]

	1985 actual	1986 estimate [1]	1987 estimate [3]
NCI	$26,874	$40,668	$47,151
NHLBI	9,323	10,718	17,091
NIDR	97	1,712	2,733
NINCDS	1,168	1,435	1,575
NIAID	23,273	61,430	67,520
NICHD			674
NEI	200	96	104
DRR	2,802	1,657	6,142
OD		[2] 3,041	
Total, NIH	63,737	120,757	142,990

[1] Amounts available after sequestration, rescission, and planned allocation of OD appropriation.

[2] Temporary reserve.

[3] AIDS funding centralized in OASH; amounts indicate anticipated reimbursements to the Institutes.

Mr. **Early**. How much did sequestration cut the AIDS funds in 1986 in your Institute?

Dr. **Fauci**. The figure goes from $27,067,000 to $25,903,000, so, approximately a $2 million reduction.

Mr. **Early**. Will the $2 million come out of discovery or education? Or will it be spread over the two?

Dr. **Fauci**. It will be spread.

Mr. **Early**. How much in AIDS is proposed for rescission?

Dr. **Fauci**. Zero in our Institute, but $13.9 million from the OD appropriation for AIDS research.

Mr. **Early**. What proportion of AIDS research is being conducted in-house at NIH?

Dr. **Fauci**. We have a substantial number of intramural activities relating to the development of antiviral drugs, to molecular biology of the virus, to vaccine development, and to studies of the effect of the virus on the immune system. There are many areas of research. It is quite a substantial activity.

Mr. **Early**. What proportion is supported by contract?

Dr. **Fauci**. We have about $8 million out of the $25,903,000—about one-third.

Mr. EARLY. Are you satisfied with the communications back and forth to your office? Communication as far as what is going on elsewhere?

Dr. FAUCI. Very much so.

Mr. EARLY. And what proportion is being supported by grants?

Dr. FAUCI. Again, $8,151,000 of the $25 million, so that is approximately the same as the contracts. It is about one-third.

Mr. EARLY. To what extent are you able to use the regular research grant programs to support the AIDS research program?

Dr. FAUCI. We award AIDS grants through the usual mechanism of investigator-initiated grants, which are evaluated and paid on the basis of priority score. We also use our selective pay mechanism in the case of grants that are felt to be meritorious but fall below the payline. We are able to raise them for payment through this mechanism.

Mr. EARLY. Do the funds earmarked for AIDS have to go through the regular peer review process?

Dr. FAUCI. Yes, they do, sir.

Mr. EARLY. Are we supporting marginal or inferior research just because it relates to AIDS?

Dr. FAUCI. No, not at all, sir.

Mr. EARLY. For the record, I would like you, in your professional judgment, to give us an estimate of when we will complete the discovery stage, and when we will complete the animal testing.

Dr. FAUCI. Fine.

[The information follows:]

TIMEFRAME FOR DEVELOPMENT AND TESTING OF THERAPEUTIC AGENTS AGAINST AIDS VIRUS

The NIAID/NCI program for the development and testing of therapeutic agents against the AIDS retrovirus is a dynamic process in which drugs will be synthesized in the laboratory or discovered through screening of existing compounds followed by preclinical and finally clinical testing in humans.

It is not possible to predict the amount of time in which a drug will be created through research in drug discovery groups; however, it would presumably be related to the number of such groups involved in this type of basic developmental research. By the same token, one cannot predict the exact time that a drug would be discovered through the screening process. The program will involve a comprehensive screening program of thousands of existing compounds. Obviously, the more compounds screened, the greater the chance of finding one or more with anti-HTLV-III activity in the test tube.

Once a drug has been created or discovered to have antiviral activity in the test tube, it would move into preclinical pharmacologic testing and toxicity testing in animals. Although this process would take 1½ to 2 years, it is possible to obtain sufficient information within six to nine months to proceed to initiate Phase I studies.

Review of the preclinical data by the NIAID/NCI AIDS Drug Selection Committee and filing of an Investigational New Drug (IND) Application with the FDA could be completed within one to two months.

It is estimated that Phase I and Phase II clinical testing would each require about one year and Phase III efficacy trials approximately two to three years.

Following this timetable, therefore, it is estimated that the time from the creation or discovery of a compound with antiviral activity until it is available for general use would be approximately five to six years. At any one point in time, it is expected that there will be a number of drugs at various stages in this process.

As has been previously mentioned, a number of drugs such as suramin, ribavirin, HPA-23, azidothymidine and Foscarnet are undergoing Phase I/II testing at the present time.

Mr. **Early**. You know, I think you three know as much as anyone in the world. On the treatment evaluation, give us your best estimate for a concluding day.

Dr. **Fauci**. I will.

Mr. **Early**. We are going to discuss the other diseases, in addition to AIDS, because they are just as important. I was just concerned about the reorganization of the AIDS money.

I will yield now to Mr. Conte.

AIDS—COFACTORS

Mr. **Conte**. Thank you.

I have been reading about some of the possible cofactors in the development of AIDS. Can you tell us what these cofactors are, and what role they play in the disease?

Dr. **Fauci**. A cofactor is something that does not, in and of itself, cause the disease but can act with the virus to induce the disease. For example, if someone had another type of infection, such as with the Epstein-Barr virus, at the same time that they were exposed to the AIDS virus, the other infection might be a cofactor. Certain drugs that individuals take may serve as cofactors. Even certain genetic factors may serve as a cofactor. A cofactor is something that would help the HTLV-III/LAV virus cause disease. We are conducting very active studies on cofactors.

AIDS—VICTIMS

Mr. **Conte**. We talked a little last year about the potential spread of the disease out of the high risk groups and into the general population. Since then we have gotten the blood tests into mass use, and the Public Health Service has issued broad guidelines for handling victims.

What growth are we seeing in a number of people outside the high risk groups that are coming down with AIDS, and what does the discovery that AIDS can be transmitted from women to men and vice versa tell us about the future?

Dr. **Fauci**. The risk groups to which you refer are male homosexuals, intravenous drug abusers, recipients of transfusions, and hemophiliacs receiving Factor VIII.

Although the numbers in all those groups have increased, the relative proportions have stayed the same. Although heterosexually transmitted cases are still staying at 1 percent of the total cases, there is concern, and I think based on some good data, that the relative proportion will begin to increase. We are concerned about that, Mr. Conte.

PERTUSSIS VACCINE

Mr. **Conte**. Last year, when you were up here, there was a lot of trouble going on with regards to the DPT vaccine, both in terms of supply and safety. In your justifications, I read that you are working with researchers in Sweden to come up with a safer version of the whooping cough vaccine.

Dr. **Fauci**. Yes, sir.

Mr. CONTE. Do you have anything to report on the progress of that trial, and if this one does not prove effective, do we have any alternatives to turn to?

Dr. FAUCI. The trial to which you are referring is a trial of two Japanese acellular pertussis vaccines. "Acellular" means that it is in a reasonably purified form. Since the trial only began on February 3, 1986, we have nothing to report to you at this time. Hopefully by next year, we will be able to give you some indication of the safety and the efficacy of these vaccines. If it works, Mr. Conte, I think that we will be home free. The problem is that if it does not work, we may have to go back to the drawing board. Using the basic research that is ongoing, even in our own intramural program, we would have to try to test another approach, such as a molecular biological approach.

Mr. CONTE. Well, I hope I am around here next year to hear you.

Dr. FAUCI. I hope so, too.

Mr. CONTE. In your professional opinion, are we doing everything we should be doing to develop a safer pertussis vaccine?

Dr. FAUCI. As I said, if we hit the nail on the head with the Swedish trial, then we are in good shape. If not, then we should put more effort into it.

THE COMMON COLD

Mr. CONTE. At the beginning of the year a lot was made in the press about the claims that interferon was a cure for the common cold. I have not seen much around recently about this. What role can interferon play in attacking the common cold, and why is it that we cannot get a hold on this disease?

Colds are probably the main cause of visits to the doctor in this country.

Dr. FAUCI. The study that you are referring to involved spraying interferon into the nasal passages of individuals who were in a setting where they would be exposed to the common cold. Their acquisition of colds was compared with individuals who did not receive the nasally administered interferon.

The individuals who received the interferon spray were protected against colds to a significantly greater extent than were individuals who received a placebo.

Nasal sprays are not a very practical way to stop the spread of a common cold. The difficulty with the common cold is that, although we call it the "common cold," there are many, many variants of viruses that cause it—rhinoviruses, parainfluenza viruses, all types of viruses. If there were only one, we could nail it down and you would not have to worry about the common cold. However, as the situation exists, if you were vaccinated against one strain of virus, and a couple of months later someone sneezed on you in the elevator with another strain, you would have another cold.

So it is a tough story.

RESEARCH ON SEXUALLY TRANSMITTED DISEASES

Mr. CONTE. In 1980, Doctor, a sexually transmitted disease study group at your Institute made recommendations for future funding of STD research. What levels did they suggest and how well have you been able to hold to those recommendations?

Dr. **Fauci**. Well, I do not have the exact levels recommended by that sexually transmitted disease study group, but I can tell you that recently we established another sexually transmitted disease research unit at the University of Texas at San Antonio, which brings our STD research units now to a total of six.

Mr. **Conte**. Are we spending enough money in this area?

Dr. **Fauci**. Well, "enough," is when you have the problem solved. I think that we are doing a good job in the area of sexually transmitted diseases.

CHLAMYDIA

Mr. **Conte**. One STD that has gotten more attention recently is chlamydia. It affects 3 million people a year, with young people at the highest risk. What are you doing to find a solution here?

Dr. **Fauci**. We have a number of ongoing research projects. One that is of interest from a general public health standpoint is the rapid diagnosis of chlamydia. Chlamydia is a much under-appreciated sexually transmitted disease that can very often be asymptomatic, such that a woman or a man may not know that they have it and yet can transmit it to another person. This has very important implications and not only for the individuals involved. It can also be transmitted to a child during passage through the birth canal.

Mr. **Conte**. How would a potential mother find out about it?

Dr. **Fauci**. Using molecular probes, one can diagnose in the doctor's office in just a few hours, whether an individual is infected.

I think the rapid diagnostic procedures have led to a recent appreciation of, as you said, the fact that there are 3 million cases in this country per year. We are now aware that this is a major problem. We were not aware of it before, because much of the disease was asymptomatic.

Now, we are aware of the disease; we have a mechanism of rapid diagnosis; and the treatment of it is not difficult at all. It is really a question of patients realizing that they have the disease. I think that we have made significant headway in this area.

Mr. **Conte**. What do you use as a cure, penicillin?

Dr. **Fauci**. It is a more broad-spectrum antibiotic. It is a tetracycline-type antibiotic.

AIDS RESEARCH—USEFUL KNOWLEDGE FOR OTHER DISEASES

Mr. **Conte**. The push has been on now for 4 years to come up with the answer to the AIDS virus. Generally speaking, has the emphasis on AIDS research negatively impacted our efforts to look at other sexually transmitted diseases?

Dr. **Fauci**. No, I do not think so. I think the scientific approach that has been taken toward AIDS has really allowed us to gain even more knowledge in other areas, both in infectious diseases and in immunology. It is one of those unusual diseases that opens up a lot of doors in biomedical research.

The overlap and impact on other areas is extraordinary. Thus, in fact, it has been a plus for other research.

ASTHMATIC ATTACKS

Mr. CONTE. You can put this answer in the record, if you like. I understand that we are learning a lot more about the mechanisms of how people get asthmatic attacks, and there exists the possibility of ultimately controlling these attacks by manipulating the immune system. Can you explain for us what is being done to regulate and control the abnormal immune response that is responsible for certain cases of asthma.

Dr. FAUCI. Yes, I will provide the information for the record.

[The information follows:]

ASTHMATIC ATTACKS

It is now evident that asthmatic attacks can be triggered in several ways and that, on this basis, there clearly are different groups of asthma patients. Most asthmatics, however, are less responsive than normal individuals to a nervous system stimulus that causes muscles in the airways to relax and allow unrestricted breathing. Recent evidence indicates that some patients actually have formed immune responses (auto-antibodies) against the nerve signal receptors on airway muscle cells. These auto-antibodies can interfere with the normal process that controls airway opening and may explain the asthmatic's reduced respiratory response to nervous stimulation. A means to ablate these auto-antibodies is being actively pursued; hopefully some of the newer immunoregulatory approaches may be applicable.

Inhalation of allergens to which patients are sensitive represents another means to provoke asthmatic attacks. In patients who have formed IgE antibodies against an allergen, a cascade release of inflammatory molecules, including histamine, occurs when such antibodies react with the allergen, leading to respiratory distress. The use of carefully controlled immunization with the allergen, or immunotherapy, is one way to reduce or remove an individual's sensitivity to the allergen. In this case, immunotherapy induces the formation of blocking antibodies that interfere with the reaction of the allergen and IgE antibody and prevents the inflammatory cascade from developing. The NIAID is currently supporting cooperative clinical trials of immunotherapy in asthmatic patients sensitive to animal products, house dust mites, or ragweed to evaluate this approach to regulating IgE antibody reactions as a routine therapeutic modality for allergic asthma. Also, NIAID is supporting studies of other approaches to inhibit IgE-induced asthma. This research includes efforts to develop allergen tolerance by immunization with chemically modified allergens and to evaluate means for reducing IgE reactivity using anti-IgE antibodies or immunoregulatory molecules, such as IgE suppressor factor.

Mr. EARLY. Mr. O'Brien.

FUNDING FOR FOREIGN AWARDS

Mr. O'BRIEN. Mr. Chairman, Doctors, several years ago, I think the Institute reported something on the order of $200 million in grants for research in Australia, Canada, Finland, France, Israel, Switzerland and the U.K. An overview of the types of research sponsored by the Institutes in these other countries would be helpful. Is research coordinated through an international agency? Is there an NIAID or an NIH agency that passes on or examines foreign research applications?

Dr. FAUCI. The NIAID has not awarded such a funding level of foreign grants. I think what they were referring to is that the NIAID funds grants for work, for example, in parasitic diseases. But we have not provided that amount of money—$200 million—for foreign grants.

Dr. WYNGAARDEN. The total figure for the NIH has been about 1.5 percent of our budget every year for the last 10 to 20 years. Of that, roughly half is in grants to foreign countries, and the other half is in training and conference and travel funds for our scientists.

The figure this year is $75 million altogether, with about $37 or $38 million of that in grants.

Dr. Fauci. For our Institute, NIAID, the total support for foreign awards for FY 1985 was $728,000.

Mr. O'Brien. Well, I had a few more questions that I might ask you to write answers for the record, doctor.

Dr. Fauci. Fine.

Mr. O'Brien. You are a good witness, thank you.

Thank you, Mr. Chairman.

Mr. Early. Thank you.

Mr. Early. Mr. Porter.

CHRONIC EPSTEIN-BARR VIRUS

Mr. Porter. Recently the chronic Epstein-Barr virus has been identified in people in Lake Tahoe, California, Harrington, Nevada, Takoma, Washington and a New England office building, I am told.

What have you done to investigate and study those reports so that you can learn from these outbreaks of the chronic disease?

Dr. Fauci. We are not sure about all of them, but I am very interested that you brought this up. You must really be up on the latest scientific literature, because this is something that we have only recently heard about.

We know that chronic Epstein-Barr virus disease causes a very vague syndrome of malaise and fatigue. It has been a very illusive syndrome to study because it is so difficult to diagnose. The clue that it is caused by EBV is that if you look at the antibody tests, they indicate that an individual is going through an acute or a subacute reaction to this virus.

The Lake Tahoe cases that you mentioned have been referred to our intramural program. When individuals have this chronic type of syndrome, the only abnormality that they have is an elevation of antibodies against EBV. This is very, very interesting because the condition seems to be spreading rapidly, probably by the respiratory route. We are going to bring some of those individuals into our intramural research program at the Clinical Center in Bethesda, to study them and to determine, if, in fact, they do have chronic EBV infections. If they do, then we will approach it from there; but if not, I think it will be very interesting to see what they do have.

Mr. Porter. Could this be simply an incidence of a doctor diagnosing something that other doctors are not diagnosing, as well, rather than something that is particular to the area?

Dr. Fauci. I would think that is one possibility. But given the fact that these cases were so dramatic, I am wondering whether it was really something indigenous to that area. That is the reason our red flag went up and we are going to investigate it.

Mr. Porter. It should be a source of good information.

Dr. Fauci. Oh, absolutely, absolutely.

CONFERENCES ON EPSTEIN-BARR VIRUS

Mr. **Porter**. I am not sure if this is something that will be in your jurisdiction or not, but what have you done to establish a protocol for physicians to record the incidence of chronic Epstein-Barr virus?

Dr. **Fauci**. We have had a workshop meeting at the NIH led by one of our intramural investigators, Dr. Stephen Straus, who is one of the leading investigators in this field. He has studies on Epstein-Barr virus ongoing at the Clinical Center. The workshop was concerned with criteria for the diagnosis of this syndrome. I cannot emphasize too strongly how difficult it is to get a handle on this disease if there are no accepted criteria to diagnose it.

That workshop attempted to establish some solid criteria so that we can identify cases that would otherwise have been missed.

Mr. **Porter**. In April of 1985, there was a workshop held that apparently was attended by many EBV researchers and considered to be a very informational and worthwhile workshop on the disease.

Are there any future meetings of this type planned?

Dr. **Fauci**. I do not know that, Mr. Porter, but I can get that information for you. The workshop to which you refer was held last spring at the NIH.

Mr. **Porter**. Fine.

[The information follows:]

Conferences on Epstein-Barr Virus (EBV)

The workshop on Chronic Infectious Mononucleosis that was held in April 1985 was unique in that it was the first conference organized solely on the chronic forms of Epstein-Barr virus infections. No sequel to this workshop has been planned to date, but three other conferences in 1986 will include topics on EBV infections:

1. *The Second International Symposium on Epstein-Barr Virus and Associated Malignant Diseases* is to be held in St. Petersburg, Florida on October 17-22, 1986;
2. *The Eleventh International Conference on Herpesviruses* is to be held in Leeds, England on July 21-26, 1986; and
3. *The Annual Meeting of the American Society for Virology* is to be held in Santa Barbara, California on June 22-26, 1986.

Conferences on specific diseases such as chronic EBV about which relatively small numbers of investigators are concerned are most productive when held no more often than every two or three years. This interval allows scientists sufficient time to gather significant new information for sharing with their colleagues. More frequent conferences are often encumbered with redundancies. For this reason, a second workshop specifically on chronic EBV is unlikely to be scheduled before 1987.

EPSTEIN-BARR VIRUS RESEARCH COLLABORATION

Mr. **Porter**. Is NIH cooperating with any pharmaceutical companies in EBV research and are there any results available?

Dr. **Fauci**. The investigational drug, DHPG, which stands for dihydroxy propoxymethyl guanine, is being used to treat life-threatening EBV infections. A large, two-year, controlled clinical trial is beginning at the NIH Clinical Center in which acyclovir will be used to treat EBV infections; this study is a joint venture of NIAID and Burroughs Wellcome.

CHRONIC EPSTEIN-BARR VIRUS

Mr. **Porter**. Does an individual have to have had the infectious form of the disease before they might suffer from the chronic form?

Dr. **Fauci**. That is a very good point, because as I mentioned earlier, virtually everyone in this room has been infected with this virus. However, only a small percentage of us know it because we got sick. If you analyze blood samples, you will find that almost all of us have antibodies indicating exposure to the virus at some time.

The answer to your question is yes, you would have to be infected with it, but you do not have to get sick with it in order to develop the chronic form. You can get the chronic form without having had the acute EBV syndrome. That is why the chronic form of the disease is so elusive, because there is no direct relationship between one and the other. This is an area of considerable confusion for practicing physicians.

Mr. **Porter**. It seems that the more that we find out about some viruses, the more we find new ones. We never seem to catch up. Is it an unending process when we always find new ones?

Dr. **Fauci**. Yes. And that is a good reason for having the National Institute of Allergy and Infectious Diseases.

NUTRITION AND INFECTIOUS DISEASES

Mr. **Porter**. I asked this last year and I want to follow-up on it. What studies are currently being conducted to examine the relationship between diet and prevention of infectious diseases?

Dr. **Fauci**. All right.

Mr. **Porter**. What progress has been made?

Dr. **Fauci**. We have been able to show, for example, that in infants with infectious diarrhea, feeding them a certain type of oral rehydration not only replaces the life-threatening fluid loss, but actually helps to stop the infectious diarrhea. That is just one example of how a nutritional component can have an impact on infectious disease. There are also a number of ongoing studies investigating the effect of malnutrition on the immune system or on the ability of the body to specifically fight certain organisms. That is an area of great importance worldwide and even in certain segments of our own population.

Mr. **Porter**. What percentage of your budget is spent on nutritional studies?

Dr. **Fauci**. The estimate for FY 1986 is $1,659,000.

Mr. **Porter**. So it is fairly small?

Dr. **Fauci**. Yes.

Mr. **Porter**. Is that not an area where there is real promise? We spend a lot of our resources fighting specific things that we know about, but should we not really spend more time and money preventing and finding ways of preventing those viruses?

Dr. **Fauci**. The point you make is a good one. Our main prevention approach, Mr. Porter, is however, in vaccine development. We have a substantial commitment in that area. I believe as basic science more clearly delineates the relationship between nutrition and infectious disease, we will take the opportunity to pursue nutritional factors in disease prevention. In the normal course of events, nutrition in the vast majority of the population, has very little impact on susceptibility to infectious diseases. It is only in a certain subset of the population and only when we are able to dissect out more fully just what the relationship is, that avenues of further research will open. At that time, we will take that opportunity to pursue it.

Mr. **Porter**. Thank you very much, Doctor.

Thank you, Mr. Chairman.

FY 1987 BUDGET

Mr. **Early**. Doctor, again, the emphasis has been on AIDS and I do not want you to think that this is any more important than the other programs.

What was your budget request to Dr. Wyngaarden?

Dr. **Fauci**. Our budget request to NIH was $493,044,000.

Mr. **Early**. With the AIDS money that is now, so to speak, being transferred?

Dr. **Fauci**. Yes. Not all of the AIDS funding was included. The 1986 new initiatives were not included—just our base money.

ELIMINATION OF RESEARCH PROJECT GRANTS

Mr. **Early**. Fine.

Doctor, with your new and competing research grants, there are 62 fewer.

Dr. **Fauci**. Yes.

Mr. **Early**. Can you, for the record, tell us what areas of research that will be eliminated?

Dr. **Fauci**. The 62 fewer grants are part of the proposed rescission. Yes, I will provide that for the record.

[The information follows:]

Elimination of Research Project Grants

The 62 research project grants that will not be funded under the rescission will largely be determined by priority score. Therefore, they may fall within any of the grant-supported activities of the Institute, and may include basic research in asthma and allergic diseases, the immune system and its disorders, genetics and transplantation biology, a wide variety of bacterial, viral and parasitic diseases, and vaccine and antiviral drug development.

REPROGRAMMING REQUEST

Mr. **Early**. Will the Institute seek a reprogramming request to accommodate the Gramm-Rudman-Hollings reductions?

Dr. **Fauci**. We have not requested reprogramming at this time, but we might do so later upon looking at the total impact of the reductions on our programs.

GRANT AWARD RATE

Mr. **Early**. Without the rescission what would your approved grant rate be, what percent?

Dr. **Fauci**. Without the rescission, our award rate would be 32.6 percent.

Mr. **Early**. What does the 1987 budget have for its percentage of approval?

Dr. **Fauci**. In 1987 the award rate is estimated to be 26.7 percent.

Mr. **Early**. How does that compare to 1985?

Dr. **Fauci**. In 1985, it was 36.5 percent.

Mr. Early. You have 36.5 and now you go down to 28, that is infringing on your autonomy is it not?

Dr. Fauci. That is making it difficult to fund certain grants.

DOWNWARD NEGOTIATIONS

Mr. Early. What is your professional opinion of a downward negotiation of almost 10.5 percent for competing and noncompeting grants? What effect is that going to have on these grants?

Dr. Fauci. Well, it will reach a point of diminishing returns. If you downward negotiate so much, you will get to the point where you will be ineffective in carrying out the goals of the grant. When you do reach that point, you are getting into a danger zone.

Mr. Early. I personally do not think that the directors are suggesting what that point of diminishing return is.

What do you think that point is?

Dr. Fauci. I think it is likely not to be 13 percent. It is less than 10 percent. I think that when you get to 10 percent, you are getting into some trouble.

AIDS—STAFF

Mr. Early. Doctor, let's get back to AIDS.

Are the employment ceilings restricting the intramural AIDS research program?

Dr. Fauci. As we have mentioned before, in our intramural program we have had to move staff around, redirecting or absorbing them out of other programs into the AIDS research effort.

AIDS—CLINICAL TRIALS

Mr. Early. How many AIDS patients are being treated today in clinical trials, doctor, that you are aware of?

Dr. Fauci. In official clinical trials, there are several hundred throughout the country.

Mr. Early. And does the information get back to your Institute?

Dr. Fauci Yes, it does.

Mr. Early. Are you satisfied that you can see the developments in each stage?

Dr. Fauci. I am looking forward with great anticipation to the opening of our AIDS Treatment Evaluation Units, which will be established this summer. I think they are going to have a major impact on our ability to test new agents against AIDS in treatment protocols.

AIDS VICTIMS

Mr. Early. What, in your professional opinion is the threat of AIDS? I have heard some say, that it is similar to the threat of bubonic plague. And some will say that it is exaggerated, and I am not sure.

I do not want to scare people but in your statement you said, "the five-year projected fatality for persons with full-blown AIDS still approaches a 100 percent."

Dr. Fauci. It is a very serious problem given the fact that at least 1 million people in this country are infected with the virus.

Even if we were to control the epidemic right now, given the projection of how many of the infected individuals will develop full-blown disease, you are talking about hundreds of thousands of people with the disease.

Mr. EARLY. Doctor, do you have a statistic you can use to say how long it is from the time of discovery to death?

Dr. FAUCI. Yes.

Mr. EARLY. What is it?

Dr. FAUCI. If you have an opportunistic infection, such as *Pneumocystis carinii* pneumonia, the mean time from the time of that first pneumonia to death is between 35 and 40 weeks. If all you have is Kaposi's sarcoma, the mean time of death is between 12 and 18 months.

Mr. EARLY. That is frightening.

Dr. FAUCI. It is.

AIDS—HETEROSEXUAL TRANSMISSION

Mr. EARLY. Doctor, Dr. Haseltine and Dr. Essex have been discussing with me this particular problem. They suggest or suspect that an unbelievable number of prostitutes in New York are AIDS carriers.

Have you heard that?

Dr. FAUCI. Yes, the number is between 40 and 70 percent of street prostitutes.

Mr. EARLY. Do they spread that as quickly as I think they do?

Dr. FAUCI. It depends on their business. This relates to the point that I made earlier. I strongly believe that we are going to see heterosexual transmission from female to male, and we will first see it in relation to spread by the prostitute population. That does not mean that it will be a very effective form of transmission or that every female prostitute who is infected with the virus will, in fact, be able to transmit it to her partners.

But I think that given the large percentage of those individuals who are infected, we are faced with a potentially very serious problem.

Mr. EARLY. But can you guarantee us that it does not spread with each act?

Dr. FAUCI. I cannot guarantee that at all.

Mr. EARLY. And do you have any studies that show the likelihood of transmission is related to the degree of AIDS the carrier has?

Dr. FAUCI. That is still unclear at this time. There are ongoing studies in Africa, which are showing that the ratio of contact to actual development of infection is very high in that population, and we are currently doing studies to determine if there are other cofactors in Africa that may or may not be present in the United States.

I think the United States Armed Forces will be a very good source for these kinds of studies. This is something that I have discussed with military officials myself. We have discussed possible studies of the antibody positivity rates of prostitutes in ports into which military personnel go, followed by observations of seroconversion rates in troops.

Such a study will probably be initiated reasonably soon.

Mr. **Early**. I have seen the numbers on the prostitutes in Germany that have antibodies to the AIDS virus and it was up to 90 percent for the ones that were not regulated.

Dr. **Fauci**. Yes, street prostitutes as opposed to——

Mr. **Early**. Yes, 90 percent, which gave the suggestion, I think, that they are only unregulated because they are on drugs.

Are we getting there quick enough?

Dr. **Fauci**. Yes. I do not think that we need to wait for results from studies in order to direct our thinking and our efforts toward the probability that there is heterosexual transmission. The studies will take a couple of years to complete. Based on the evidence that the virus is in a large segment of the prostitute population and on the early data from the Armed Forces studies, it is clear that the possibility of heterosexual transmission is a reality.

AIDS—FUNDING

Mr. **Early**. I appreciate your answer, doctor.

Tell me, in your professional opinion, are we spending too much on AIDS?

Dr. **Fauci**. In my professional opinion, we are not spending too much on AIDS.

Mr. **Early**. Are we spending enough, are we missing anything that is new?

Dr. **Fauci**. At this time, given what we would presume to be our allocation, we would be able to do everything that I feel from the basic research standpoint, should be done. Within the auspices of our Institute and the NIH, we would have enough money.

AIDS TREATMENT

Mr. **Early**. In your professional judgment, how many years away are we from an effective treatment for AIDS?

Dr. **Fauci**. That is a difficult question. I hope that we will be able, in less than a year, to have a number of drugs under study in our AIDS Treatment Evaluation Units. I also hope that within a year to a year and a half, we will be able to have something that shows some treatment value, but that is purely an estimate Mr. Early.

Mr. **Early**. In addition to the four or five drugs you identified, how many do you expect to conclude with?

Dr. **Fauci**. In addition to the five I showed you, there are 29 other drugs that are ready to go into some study phase. A significant number of drugs have gone through the AIDS Drug Selection Committee.

AIDS DRUG SELECTION COMMITTEE

Mr. **Early**. With all the problems that are noted here, why shouldn't we skip that committee, and get to the treatment evaluation?

Would it not be the proper thing to do? I think that everyone establishes committees, doctor, to avoid being criticized.

Dr. Wyngaarden, would you have problems with you, Dr. Fauci, and Dr. DeVita, being the——

Dr. Wyngaarden. Significant clinical expertise is required in drug evaluation and in evaluating the studies that are done. The members of that committee have had extensive experience in drug evaluation for other purposes, such as cancer therapeutic agents. That is an art form that one does not develop by looking at statistics occasionally; one must work very hard on that.

Mr. Early. That is an established committee today?

Dr. Wyngaarden. Yes, it is the drug selection committee and it has been in business for some time.

Dr. Fauci. Yes, it has been very helpful. It consists of a group of individuals from our Institute, NIAID, and from the Cancer Institute and others.

Mr. Early. So it is not the creation of a new——

Dr. Fauci. No, I am sorry that you got that impression. The Drug Selection Committee is a part of the collaborative effort between Dr. De Vita's Institute and our Institute.

CHLAMYDIA

Mr. Early. Doctor, I thought chlamydia was just a woman's disease?

Dr. Fauci. No, it is not.

Mr. Early. Is that new?

Dr. Fauci. No, that is not new. Women have to get it from somewhere and they get it from men.

Mr. Early. You do have to blame us for everything?

Dr. Fauci. The reason it was not recognized in men is that most of the time it was either asymptomatic in men or it was thought to be gonorrhea, and inappropriately treated as gonorrhea. We only realized that it was not gonorrhea when it did not respond to the classic gonorrhea treatment. Women can develop classic, chronic pelvic inflammatory disease as a result of chlamydia infection so it is more obvious in women.

ACCELERATED DEVELOPMENT OF NEW VACCINES

Mr. Early. Doctor, bring us up to date on the status of your accelerated development of new vaccines?

Dr. Fauci. As you have heard in the past, we asked the Institute of Medicine to prioritize a number of vaccines for us with regard to the need for research and development in that area.

Mr. Early. How many vaccines?

Dr. Fauci. They considered 14 disease pathogens for analysis by the domestic model and assigned the highest priority to five vaccines in the following order: hepatitis-B virus; respiratory syncytial virus; *Haemophilus influenzae* type b; influenza; and varicella. I will provide you with a status report for the record.

Mr. Early. Fine.

[The information follows:]

STATUS OF PROGRAM FOR THE ACCELERATED DEVELOPMENT OF NEW VACCINES

Subsequent to the initiation of this program in 1981, the Institute targeted 10 diseases or disease categories caused by 17 different organisms for prevention by immunization with new or improved vaccines within the next 10 years, some by 1990. Their status follows:

1. Meningitis in infants (H. influenzae type b) - A polysaccharide vaccine has been licensed for use in children 24 months and older. A protein-polysaccharide conjugate vaccine for use in younger children is undergoing efficacy trial.

   (Group B streptococci) - Candidate polysaccharide antigens have been developed for important serotypes; more research is needed to determine immunogenicity in target populations and consistency of antigenicity of different lots of vaccine.

2. Gonorrhea - A protein I gonococcal vaccine has been shown not to protect males against intraurethral challenge with a virulent gonococcal strain, despite a good serum antibody level raised against the P-1 antigen. Another candidate vaccine consisting of synthetic peptides of the conserved domain of the gonococcal pilus combined with an iron-regulated protein of the gonococcus is under consideration for Phase I testing in volunteers.

3. Croup and Pneumonia in Infants (Respiratory Syncytial Virus) - Nucleotide sequences for major glycoprotein (G) and fusion protein have been obtained. Genes coding for these antigens have been cloned and sequenced. A vaccinia virus recombinant containing the G gene protected cotton rats against intranasal challenge with virulent RSV.

   (Parainfluenza Virus) - Two surface glycoproteins, one combining the hemmagglutinin and neuraminidases (HN), and the other the fusion protein (F), have been purified.

4. Whooping Cough (improved Bordetella pertussis) - Acellular vaccines have been produced in several countries. Vaccines containing one or more components are to be tested for efficacy in Sweden, and, if possible, elsewhere. A DNA fragment has been cloned which contains at least two genes responsible for expression of pertussis toxin, providing the basis for a recombinant "third generation" vaccine.

5. Influenza (live, attenuated A) - Surface antigens (HA & N) from wild viruses have been repeatedly transferred via gene reassortment to an attenuated influenza A master strain. Live vaccine has been shown to be safe and effective when administered as nose drops. Tests are in progress in young children and in the elderly.

   (B) - Candidate influenza B attenuated master strains have been developed. Volunteer studies are needed.

6. Diarrhea (Cholera) - Live oral vaccines containing genetically engineered strains lacking a subunit toxin gene have protected over 80 percent of volunteers against challenge, but have mild residual toxicity. A number of other strains with precise genetic lesions await testing. A field trial of combined B subunit plus killed whole cell oral vaccine is in progress in Bangladesh.

   (Typhoid) - A mutagenized, enzyme-deficient strain of Salmonella typhi (Ty21a) has shown varying degrees of efficacy when administered as a live oral vaccine in Egypt (95 percent) and Chile (0 to 80 percent). Other auxotrophic, nutritional mutants await testing in volunteers.

   (Dysentery - Shigella sonnei) - Army scientists have inserted plasmid gene coding for the protective antigen on S. sonnei into Ty21a vaccine strain of S. typhi. This hybrid live vaccine protected 53 percent of challenged volunteers against diarrhea and 100 percent against significant fever.

   (Shigella flexneri) - Army scientists have transferred S. flexneri 2a gene loci related to virulence markers to E. coli K12. The hybrid live vaccine was effective in a monkey model; volunteer studies are planned.

   (Rotaviruses) - Live oral vaccines made with viruses from two heterologous species have been shown to be safe and immunogenic in children. A bovine rotavirus strain (RIT4237) protected infants against severe rotavirus diarrhea in Finland but did less well in other trials. A rhesus rotavirus has been shown to be capable of infecting infants even in the presence of maternal antibody. Bovine and rhesus vaccines are being tested concurrently in a field trial on a U.S. Indian reservation and separately in other populations.

7. Hepatitis (A) - The hepatitis A picornavirus has been shown to share molecular features with other enteroviruses such as polioviruses. Approaches to inactivated and live vaccines similar to those used for polio are in progress. A live virus attenuated for chimpanzees and marmosets has been administered safely to a small number of adults (Merck). Another live virus vaccine developed at NIAID is expected to undergo clinical testing in 1986. An activated vaccine developed by Army scientists is scheduled for safety and immunogenicity testing.

   (Second generation B) - Several candidate vaccines containing HBsAg produced in yeast or mammalian cells using recombinant DNA technology have been shown to be safe and immunogenic. Efficacy trials in infants born to carrier mothers are in progress.

8. Chickenpox (Varicella) - A live attenuated varicella virus vaccine has been shown to be safe and effective in children with acute lymphocytic leukemia (ALL) who have been in remission for at least one year. Trials are continuing in

children with other malignancies, in children with ALL who have been in remission for at least nine months, and in normal children. The producer has applied for licensure.

9. Genital herpes - An inactivated herpes simplex type 2 subunit vaccine failed to prevent recurrent disease or to prevent transmission between sexual partners. A hybrid live vaccine produced by incorporating the herpes gene coding for protective glycoprotein into vaccinia virus has been shown to protect mice. Other candidate live virus vaccines have been produced by deleting gene segments related to latency and neurovirulence.

10. Malaria (Plasmodium falciparum) (Sporozoite) - Molecular genetics and hybridoma technology have been used to characterize the major antigenic determinant of sporozoites (the stage transmitted by the mosquito)--the circumsporozoite (CS) protein. Genes coding for the CS protein have been cloned and antigens based on repeating subunits of the CS protein have been produced by recombinant DNA or as synthetic peptides. Two vaccines have been prepared commercially and are ready for safety and immunogenicity testing in volunteers.

    (Merozoite) - Antigens from the merozoite surface, its cytoplasm, the infected RBC surface, and the culture medium have been identified, and in some cases, the relevant genes cloned. Studies on protective ability of these antigens are underway.

    (Plasmodium vivax) - A species-specific immunodominant region with repetitive epitopes has also been idenitified in P. vivax CS protein. Monoclonal antibodies to the asexual stages have been produced, some of which are stage- or species-specific while others identify antigens shared by different species.

Mr. **Early**. And could additional vaccines be included if you had additional moneys?

Dr. **Fauci**. We did not include pertussis in this group. That was considered separately; but as I mentioned before, if the Swedish trial does not work, the expansion of basic research in pertussis would be appropriate.

Mr. **Early**. You know we call it an accelerated vaccine program because it has so much potential.

Is this an in-house program or is it a primarily a grant or contract program?

Dr. **Fauci**. It is a grant and contract program predominantly. There are some in-house intramural researchers working in this area, but most of the accelerated program is supported through grants and contracts.

HEPATITIS—DELTA AGENT

Mr. **Early**. The largest city in my district is Worcester, and we have a big hepatitis problem there. Every time I read about it in the paper, I see that the CDC is in contact with Worcester. Are you familiar with it?

Dr. **Fauci**. Yes, we are.

Mr. **Early**. Has your Institute done anything with it?

Dr. **Fauci**. We have not specifically addressed the problem as it relates to Worcester, Massachusetts, but we are doing research in this area. I believe that the problem was hepatitis caused by the delta agent.

Mr. **Early**. That is right.

Dr. **Fauci**. We are doing a substantial amount of work with the delta agent. In fact, we have made some very important research advances at the molecular biological level on the delta agent. I think that the awareness of the mini-epidemic in Worcester has created even more momentum for basic research on the delta agent.

Mr. **Early**. And your discoveries, do you think that Worcester is familiar with them?

Dr. **Fauci**. I am sure that investigators in Worcester, at St. Vincent's Hospital and at the University of Massachusetts in Worcester, are familiar with them.

HERPES AND OTHER SEXUALLY TRANSMITTED DISEASES

Mr. **Early**. Yes, it is a real, real threat.

Doctor, bring us up to date, quickly on the latest research finding with respect to herpes and the other sexually transmitted diseases. I know that you spoke some with Mr. Conte, but I had a doctor in to see me from Boston City Hospital and he said, that it is not getting better, as far as the number of sexually transmitted diseases, it is increasing.

Dr. **Fauci**. That is correct. With regard to research on herpes, there are ongoing studies to determine the efficacy of various antiviral therapies. Oral acyclovir is an excellent drug that has been effective in reducing the severity of the disease as well as the number of recurrences of lesions in an individual infected with herpes.

The problem is that the treament does not lead to a permanent cure. The herpesvirus hides in cells so that the best that we have been able to do, and it has been a major advance, is to decrease the severity and the frequency of episodes. We are also testing agents to suppress this virus in newborn infants, because a newborn can get the virus by passing through the birth canal. This virus often causes very severe problems in the infant.

Our Institute is currently funding therapy trials of acyclovir for treating infants. In addition, a new molecular biological approach using recombinant DNA technology is being applied for the development of effective vaccines against herpes.

Mr. EARLY. Doctor, it has been longer to find a treatment for herpes than any other STD, is that true?

Dr. FAUCI. You must look at it from the standpoint that this is a viral STD and viral diseases historically have been very difficult to get to respond to therapy. There are only a couple of viruses for which there is effective therapy. A lot of the other sexually transmitted diseases, such as gonorrhea, syphilis, and chlamydia are more amenable to antibiotic therapy because they are not caused by viruses; they are caused by bacteria. The difficulty with herpes results from the nature of the microorganism that causes it.

Mr. EARLY. Well, because of that difficulty are you satisfied that we are doing enough with regard to herpes?

Dr. FAUCI. I hope that we will be able to increase and accelerate our efforts in antiviral drug development. This is an area of major importance to our Institute.

THE COMMON COLD

Mr. EARLY. Mr. Conte spoke to you about interferon with regard to colds, can you talk about that? Did I understand you to say that it was not financially feasible to do that yet?

Dr. FAUCI. It is really not feasible from the standpoint of the logistics, because the interferon must be sprayed into the nose at the time that you are being exposed to a cold.

The study I mentioned was a family study. When a little child had a cold, the researchers would spray interferon in the noses of the other family members and thereby stopped the spread. Given the nature of the common cold, it would be very difficult to put this into practice. You would have to spray interferon in your nose all day long because you would never know when someone was going to sneeze on you and give you a cold. While this is very useful information, this approach will probably not be the answer to stopping the common cold.

HOSPITAL ASSOCIATED INFECTIONS

Mr. EARLY. I recently visited a couple of hospital doctors for three days and I am really concerned about the spread of diseases in hospitals. Are you doing much with that?

Dr. FAUCI. Yes, you are referring to what we call hospital associated infections. We have 28 research projects at the present time studying a variety of approaches toward decreasing the incidence of these infections as well as studying the mechanisms for acquisition of hospital associated infections. They are a major problem.

Mr. EARLY. So if we release a report like they just did, with regard to deaths in hospitals, we will probably speed that up. I think from the numbers that we hear in this Committee, if you get sick, you should not go to a hospital.

Dr. FAUCI. I understand what you are saying, and it is a major problem. Five to ten percent of individuals who are in hospitals develop a hospital associated infection. Thus, there is up to a one in ten chance that you will get an infection in a hospital.

FUNDING FLEXIBILITY

Mr. EARLY. Well, that is awfully high. Doctor, again, there has been a lot of discussion in these areas about flexibility. In my view, your flexibility and autonomy is diminishing.

Do you feel—and I want you to be candid—that you are getting so many directives from Congress or the Executive Branch that you are unable to conduct a research program of the highest possible quality?

Dr. FAUCI. Well, there are things that can interfere with one's flexibility. As you know, in the funding process, there are various levels of restraint with regard to flexibility. I, as I believe do the other Institute Directors, would welcome some more flexibility.

INTERNATIONAL RESEARCH COLLABORATION

Mr. EARLY. In your opinion are we exporting our vaccines as quickly as possible?

I know their cultures do not always accept them but I saw in one of your charts the number of malaria deaths.

Dr. FAUCI. That is correct. Within my office we have an Office of Tropical Medicine and International Research, which has been extremely helpful in coordinating activities between our own research efforts and those of foreign countries. This office facilitates exchange of information and interaction with foreign scientists. Within our own Institute, we have that office; and, in addition, the Fogarty International Center at NIH is very helpful with international coordination.

Mr. EARLY. How about in Central America, doctor, are we getting any exchange that will really help? You know we go back and forth, which side is right, the Administration or the non-Administration, but are we giving them enough information or enough vaccines? Compassion, in the long run, is what those people are going to understand.

Dr. FAUCI. Our Institute works very closely with the Pan American Health Organization. We have done so through the years, and we continue to do so. They have been very helpful to us, and I believe that we have been very helpful to them in a number of areas. The most recent area of importance involves studying factors related to the spread of diseases, such as AIDS, in Central and South America in comparison to the United States.

Mr. EARLY. Dr. Wyngaarden, are you of the opinion that we are doing enough in that respect?

Dr. WYNGAARDEN. We do not have a large volume of research collaboration with Central America, but I would be able to put it in the record. There is some in South America, but the bulk of our international work is done under agreements with such countries as China, India, Japan, Israel, and Egypt. But if you look where the work outside of the United States is conducted, by far the largest volume is in Canada.

Mr. EARLY. Will you provide for the record, your expert opinion on whether we are doing enough?

Dr. WYNGAARDEN. Certainly.

[The information follows:]

RESEARCH COLLABORATION WITH CENTRAL AMERICA

Research collaboration directly between NIH and countries of Central America is very limited but highly appropriate. These countries are relatively small, have limited research infrastructures, and their resources and priorities must understandably be primarily directed to health services and disease prevention. Consequently, the interests we share with them in pursuing the solutions to tropical and infectious diseases and, indeed, increasingly the chronic and degenerative diseases facing all countries, are pursued particularly through out active participation in multilateral groups, such as the Pan American Health Organization (PAHO) and the Institute of Nutrition for Central America and Panama (INCAP). For example, under the umbrella of PAHO, countries of the Americas have committed themselves to the eradication of polio by 1990, and the Central American countries have and will be conducting vaccination campaigns as a part of this effort.

Second, NIH research collaboration with other major countries of the region, such as with Mexico, Brazil, Venezuela, and Colombia, as well as with other countries in the world with similar environments, have a direct relevance to the disease problems facing Central American countries, and they will benefit from such research.

Third, we are actively and directly pursuing ways to involve Central American countries in research strengthening and participation to the extent that their resources and emerging interests allow. The Fogarty International Center has recently established arrangements with Costa Rica whereby their young scientists can now be considered for International Research Fellowships. Similar arrangements were also recently made through the Pan American Faculties of Medicine organization in order that other Central American countries can participate in the program until such time as they might wish to establish their own country nominating committees. The Fogarty International Center has also sponsored, in cooperation with PAHO, a recent conference with these countries participating on examining the research manpower needs in the region for vector borne disease control. A conference of these countries is also to be held in the near future on biomedical research infrastructure building and strengthening.

Finally, the Gorgas Memorial Laboratory in Panama conducts research on diseases of direct relevance to the concerns of Central American countries, and cooperates with them not only in research but also in disease surveillance and the investigation of disease outbreaks. U.S. Government core support for this laboratory is provided through the budget of the Fogarty International Center. It also receives additional NIH grant and contract support for specific research projects.

Through these various indirect and direct means, NIH is adequately able to draw upon particular research opportunities available in these countries, is addressing most of the disease problems they face, and is helping them build their own research capabilities and become research partners of the future. So far as biomedical research cooperation with the Central American countries is concerned, we must ensure that all avenues of cooperation with U.S. investigators are fully open to their scientists to utilize and be responsive, as they are in a position to do so, so that their scientists can ultimately become full collaborators.

TROPICAL MEDICINE AND INTERNATIONAL RESEARCH

Mr. EARLY. Doctor, in the same vein, how much research are you conducting on tropical diseases?

Dr. FAUCI. We have a substantial effort in tropical diseases in our Institute, Mr. Early. If one considers all domestic tropical medicine and international research in FY 1985, $51,080,000 was provided to U.S. investigators who work in areas extrapolatable to tropical medicine and international research. Another $728,000 supported foreign awards for a total of $51,808,000. Therefore, we have a substantial effort.

Mr. Early. Are we reimbursed by the Defense Department or foreign aid agencies for any of this research?

Dr. Fauci. We do have collaborative efforts in the sense that we lend our scientific expertise to projects that are funded by the U.S. Agency for International Development. A typical example is the program that Dr. Wyngaarden mentioned—the Israeli-Egyptian collaborative effort. We are lending our scientific expertise, and the funding is reimbursed by U.S. AID.

Mr. Early. I do not want to put you in the public relations business, but do we get any credit in Egypt or Israel for that?

Dr. Fauci. I believe we do.

Mr. Early. Why should NIH support research on diseases that are really not widespread in the United States?

Dr. Fauci. There is a good reason for that, Mr. Early. Although many of these diseases are not major problems in the United States, they lend themselves to a type of research approach that invariably has significant impact on knowledge of diseases that are more common in this country.

From a strict basic research standpoint, we have profitted very well scientifically by studying such diseases.

In addition, because so many Americans travel around the world and come into contact with these diseases in foreign countries, these studies directly benefit American citizens. We have about 8 million citizens traveling abroad each year.

REDUCTON IN SUPPORT TO CENTERS

Mr. Early. Well, do not think that the question inferred that that was not appropriate.

The direct cost for research centers will be reduced by 4 percent. What is your opinion of that, I mean, what is the effect of that?

Dr. Fauci. When you say 4 percent in direct costs for research centers——

Mr. Early. Oh, that is for 1986. I think that it is close to 30 percent for 1987.

Dr. Fauci. It is.

I think that is going to create some significant problems for those centers. We have had to do that in addition to cutting the number of our centers from 18 to 14.

Mr. Early. Could you give me some more specific information on how that affects medium range and long range plans.

Dr. Fauci. Fine.

[The information follows:]

Effect of 30-Percent Reduction in Support to Centers

We estimate that approximately 75 percent of the NIAID's direct cost support for centers is for personnel. Thus, the imposition of a 30-percent reduction in support will immediately present the center directors with the difficult decision of either retaining experienced research and support personnel without having adequate funding for operating costs, or reducing personnel and functioning at a reduced level of activity. In either case, the NIAID's responsibility and mission in allergic and immunologic diseases will be directly affected by this reduction. In the long term, these reductions can be expected to slow the pace of research activity, knowledge acquisition, and the rapid application of research findings to clinical problems. Further, the reduced funding, in a practical sense, may cause medical scientists, now committed to research in these areas, to seek other means of support and lead them to other areas of, if not away from, scientific inquiry. The result may be NIAID's failure to maintain a "critical mass" of involved research studies in allergic and immunologic diseases, and, consequently, a slower rate of progress and discharge of NIAID's responsibilities in its mandated mission.

TERMINATION OF SUPPORT TO FOUR CENTERS

Mr. **Early**. I understand that 18 research centers are supported in 1986 and 14 in 1987.

There are no competing centers in 1987?

Dr. **Fauci**. That is correct. We are not going to renew the four centers that are coming up for competing renewal in 1987.

Mr. **Early**. Are we not renewing them because of money or because of potential?

Dr. **Fauci**. It was a result of the fact that we had to make money cuts. That is why we propose not to renew them.

Mr. **Early**. I do not see that as a savings, doctor. That is my personal view. If it still had the potential to give us results, it would be worth paying for.

Will the loss of four centers have a devastating impact on the Institute's research process?

Dr. **Fauci**. Well, the four centers to which you are referring are among our Asthma and Allergic Diseases Centers. These centers are carrying out a lot of the basic research on hypersensitivity and asthmatic diseases. Not renewing them would have an impact on our efforts in that area.

Mr. **Early**. For the record, give a little more, how much of an impact?

[The information follows:]

Impact of Terminating Support to Four Asthma and Allergic Diseases Centers (AADCs)

The NIAID currently has 13 active AADCs; the loss of 4 of these centers in FY 1987 represents an approximate one-third reduction of the Institute's focused interest on an important health problem affecting 35 to 40 million Americans.

The research activities of these centers cover a broad spectrum of disease problems. Each uses its specialized institutional expertise to pursue a defined aspect of the multiple problems associated with particular allergic diseases and asthma. Even with the current size of the program, several problem areas, such as drug and food allergy and occupational asthma, are not being actively investigated.

In terms of scientific interest, the loss of 4 centers in FY 1987 will result in reduced activity in areas concerned with the immunobiology of allergic disease and the pathophysiology of asthma. Further, because these institutional medical scientists have been active as unified groups in the center format between 3 and 11 years, the loss of established, productive centers with committed research and clinical programs also may have an impact on the investigators' personal commitment, the progress of knowledge acquisition, and the benefit to affected individuals, as well as lessening the NIAID's long-term investment and responsibility in this important area.

CLINICAL TRIALS

Mr. **Early**. How many clinical trials are under way in 1986?

Dr. **Fauci**. I can supply for the record how many are currently under way. We will have one major new clinical trial in FY 1986.

Mr. **Early**. For 1986 provide the names of each one and what stage they are in?

Just the specific trials.

[The information follows:]

TITLE AND STAGE OF EACH CLINICAL TRIAL - FY 1986

Title	Stage*
A Study of Allergy to Ragweed Pollen	2
Interferon, Immunity and Latent Viruses	2
An *in vitro* Approach to Problems of Clinical Allergy	2
Chemistry and Immunology of Streptococcal M Proteins	1
Lethal Bacteremia	1
Experimental and Clinical Allograft Unresponsiveness	2
Immune Regulation in Visceral Leishmaniasis	2
Antischistosomal Drugs Efficacy and Toxicology	2
Study of Antischistosomal Drugs	2
Human Filariasis in Colombia	2
Filariasis in Haiti	2
Prevention of Cytomegalovirus Infections	3
H. influenzae b and *S. pneumoniae* Carbohydrate Vaccines	3
Genetic Control of Antibody Responses to Polysaccharides	3
Prevention of Infections with a Bacterial Polysaccharide Immunoglobulin	2
Nosocomial Infections in Surgical Patients	2
Clinical Epidemiology - Pathogenesis of Genital Herpes	2
Cellular Immunology and Responses by Lymphokines	2
Clinical Studies of Kaposi's Sarcoma and Related AIDS	2
Prevalence and Pathogenesis of Cryptosporidiosis	2
Prophylaxis of *H. influenzae* and Other Infections	2
Immunotherapy of Childhood Asthma	2
Role and Effect of Gamma Interferon in AIDS	3
Allergens of *Aspergillus fumigatus*	2
Gamma Interferon--*Mycobacterium avium* Infection in AIDS	2
Immunotherapy for Adult Asthmatics (Sensitive to Ragweed)	2
Immunotherapy for Adult Asthmatics (Sensitive to House Dust Mites)	2
Polymerized Allergens	2
Immunotherapy in Cat-Induced Asthma	2
Complement Pathways in Normal and Disease States	2
Suboptimal Immunotherapy for Aero-Allergen Disease	2
Clinical Evaluation of Live Herpesvirus Vaccine	2
Pneumococcal Polysaccharide Reference Studies	1
Infectious Enteric Disease Studies	2
Study of Vaccines for Infectious Diseases	2
Efficacy Trials of Antivirals for Severe Herpesvirus	2
Clinical Trials for Evaluation of Antivirals	3
Treatment of Juvenile Laryngeal Papilloma with Interferon	3
Evaluate Control Measures Against Infectious Diseases	2
Treatment of Condyloma Acuminatum with Interferon	3
H. influenzae type b Vaccine in High Risk Infants	2
Development of an Acellular *Bordetella pertussis* Vaccine	1
Evaluation of Live Attenuated and Inactivated Influenza Vaccines	2
Multicenter Study of Prevention of Prematurity by Detection and Treatment of Gestational Genitourinary Infections	2

Clinical Trials for Therapy of Systemic Mycotic Diseases	2
Testing of Respiratory, Enteric and Bacterial Vaccines	2
Monoclonal Antibody Treatment of Kidney Graft Rejection	1
Evaluation of the Role of Immunotherapy in the Treatment of Laboratory Animal Allergy	2
Rimantadine or Amantadine in the Treatment of Influenza	2
Efficacy Trial of Cold-Adapted Vaccines	2
Clinical Trial of Prophylaxis of Anaphylactoid Reactions to Radio Contrast Media	2
Trial for Prophylaxis of *P. carinii* among AIDS Patients	1
Studies on the Antigens of Group B *Streptococcus*	3
Acellular Pertussis Vaccine Trial in Sweden	2
Treatment of Disease with the Interferon System	2
Immunology and Chemotherapy of Systemic Mycoses	2
Studies on Patients with Known/Suspected Parasitic Diseases	2
Pathogenesis/Chemotherapy of Herpesvirus Infections in Man	2
Pathogenesis of Infection with Intracellular Parasites	2
Phagocytic Cell Function	2
Clinical, Immunopathogenic, and Therapeutic Studies in the Spectrum of Vasculitis	2
Mast Cell Dysfunction in Systemic Mast Cell Disorders	2
Inflammatory Disorders of the Gastrointestinal Tract	2
Evaluation of Hepatitis B Vaccines	2
Evaluation of Respiratory Viruses in Volunteers	2
Studies of Rotaviruses in Volunteers	2
Clinical and Therapeutic Studies in Human Filariasis	3
Rotavirus Vaccine Trial in Umea, Sweden	2
Rotavirus Vaccine Field Trial in Venezuela	2

*1 = Planning/Design
2 = Patient Recruitment Open
3 = Patient Recruitment Closed

Dr. FAUCI. The major new trial is the pertussis acellular vaccine trial in Sweden to which I previously referred.

INTERLEUKIN-2

Mr. EARLY. Doctor, you mentioned in your statement, interleukin-2? I sense more enthusiasm for that in other places. What is your opinion of it?

Dr. FAUCI. We are actually quite enthusiastic about interleukin-2. We have been giving it to AIDS patients to reconstitute their immune response in clinical trials at the NIH Clinical Center and at extramurally supported facilities.

I am sure you have heard of IL-2 in cancer patients from Dr. De Vita, concerning Dr. Rosenberg's LAK cells. We are using interleukin-2 as one of the mechanisms for building up the depressed immune response in our AIDS patients.

We have had some encouraging early results.

Mr. EARLY. You were excited about that a year or two ago, are you still?

Dr. FAUCI. I still am, sir.

RESEARCH AND DEVELOPMENT CONTRACTS

Mr. EARLY. Doctor, on the 1987 request you support only 47 R&D contracts. How many did you have in 1985?

Dr. FAUCI. We estimate supporting about 60 in 1986.

Mr. EARLY. Sixty in 1986? And we are down to 47.

Dr. FAUCI. We awarded 94 in 1985.

Mr. EARLY Ninety-four in 1985, what effect does this unstableness have on your program?

Dr. FAUCI. For example, R&D contracts constitute the major budget mechanism for the support of clinical trials and vaccine development.

Thus, reductions would have an impact on these two areas, in addition to antiviral drug development and testing.

NEW INITIATIVES AND OPPORTUNITIES TO BE DELAYED

Mr. EARLY. Will any significant new research initiatives or opportunities be lost or delayed, in your opinion, because of the lack of funds in the 1987 budget?

Dr. FAUCI. In those three areas. Yes. We have antiviral studies that we would not be able to——

Mr. EARLY. Supply for the record, which ones are ready to go on line that you will not be able to do.

Dr. FAUCI. Certainly.

[The information follows:]

NEW INITIATIVES AND OPPORTUNITIES TO BE DELAYED

AIDS: There is a need to develop procedures to identify and quantitate the AIDS virus in a number of body tissues. This work is key to all drug and vaccine development studies. The current virus isolation procedure is extremely expensive and laborious and not highly accurate. In addition, it is not practical for determining the presence of virus in brain tissue. Since it will be necessary to develop drugs which reach the brain, we must have the ability to detect the virus in the brain. Efforts using several approaches are needed to develop better detection methods. Several diverse approaches to the development of vaccines have been proposed. These include using molecular biology to synthesize vaccines and to develop attenuated strains of the HTLV-III virus as well as to develop adjuvants to enhance the immune response to candidate antigens. While there are procedures to evaluate the anti-HTLV-III effect of potential drugs *in vitro*, these should be improved; and practical methods need to be developed to screen and evaluate drugs which have potential as immune system enhancers. The development of practical animal models is essential, and projects should be started to screen various African primates and other mammals as well as to develop a candidate mouse model similar to that used with other retroviral diseases. Basic immunologic studies are needed such as those to examine the nature of receptor sites for the virus on lymphocytes to determine whether T cell type is correlated with disease susceptibility.

SEXUALLY TRANSMITTED DISEASES: A sexually transmitted disease unit should be established that will concentrate on the area of pelvic inflammatory disease. There is also the need to establish a herpesvirus disease section in the intramural program to provide an interdisciplinary approach to studies of herpesvirus infections. Recent advances in recombinant DNA and monoclonal antibody technologies should be applied to the development of candidate vaccines against chlamydia, gonorrhea and syphilis. Phase I clinical testing should also be conducted with a currently available synthetic gonococcal vaccine, and large trials of antivirals for treatment of cytomegalovirus disease should be initiated. Basic immunologic studies are needed which can point to the development of a vaccine against the viruses causing genital warts.

HEPATITIS: A live attenuated hepatitis A vaccine is available, and there is a need to perform phase II clinical testing of this material. Using new information on the replication of hepatitis B virus, efforts should be mounted to develop targeted antiviral compounds for treatment of chronic hepatitis B infections. With the advances recently made on the molecular biology of the hepatitis delta agent, studies could be mounted on the pathogenic mechanisms of this virus which may give clues for the development of control measures.

HOSPITAL-ASSOCIATED INFECTIONS: Basic research is needed to develop methods for the prevention and treatment of post-operative infections. In addition, clinical studies of an immune globulin developed against several gram-negative bacteria often responsible for hospital-associated infections are needed.

PARASITIC DISEASES: Basic immunologic research is needed on the parasite causing giardiasis in order to improve diagnosis and treatment. Antigenic studies on strongyloides parasites should be carried out in order to develop a synthetic antigen for performing skin tests.

DIGESTIVE DISEASES: Basic research is needed on the roles of methane-producing human intestinal bacteria and pyloric campylobacter in causing a variety of gastrointestinal disorders in order to develop procedures for treatment and prevention.

CYSTIC FIBROSIS/RESPIRATORY DISEASES: A multicenter clinical study of cephalexin for its ability to prevent bacterial colonization in infants with cystic fibrosis should be initiated, as should efforts to develop a vaccine against Pseudomonas aeruginosa infections in individuals with cystic fibrosis.

There is also a need for efforts on other respiratory diseases such as the development of candidate vaccines against respiratory syncytial and parainfluenza viruses using recombinant DNA technology. A comprehensive study of respiratory diseases, as well as diarrheal diseases, in day care centers should be conducted. Studies on epidemiology and control measures for respiratory diseases would be benefited by the establishment of an Infectious Respiratory Disease Unit within the NIAID extramural program.

PERTUSSIS: There is the need for basic research on the immunology and pathogenesis of the organism causing pertussis in order to improve diagnostic procedures, and to define the role of mucosal antibody in protection and the roles of individual bacterial components in pathogenesis. This information is necessary to develop alternate vaccine candidates in the event that the acellular vaccines currently under clinical evaluation are unsuccessful. New recombinant DNA produced antigens should be tested as vaccine candidates, and the potential of antigens known as agglutinogens should be investigated for vaccine potential.

VACCINE DEVELOPMENT: Basic research is needed to develop new generations of vaccines for bacteria such as group B streptococci and pneumococci in which polysaccharide antigens are combined with carrier proteins. Research to develop well characterized adjuvants to improve the immune response to existing bacterial polysaccharide vaccines should also be initiated. Research efforts should be mounted, using the new molecular biologic technologies, to develop vaccines against organisms causing diseases such as cholera, Group A streptococci, rabies, dengue and other diseases in which traditional vaccine development efforts have been unsuccessful. A protein engineering unit should be established in the intramural program to explore the development of novel vaccine candidates through genetic engineering techniques. In addition, an intramural vaccine development unit should be established to develop vaccines needed by the public but which are not being developed by industry because they are considered unprofitable.

ASTHMA AND ALLERGIC DISEASES: Initiatives are needed for basic research on the underlying mechanisms of urticaria and angioedema and on understanding the underlying defect in the asthma triad in order to develop drugs or procedures for treatment. Basic studies of the growth of human mast cells in culture will also provide information to better understand and develop treatments for allergic diseases. A clinical study of immunotherapy in the treatment of food allergies is needed along with comparative studies of various available treatments for allergic rhinitis, sinusitis and asthma.

IMMUNOLOGIC DISORDERS: A number of basic research efforts should be initiated to better understand and treat various immunologic disorders. These include: studies on the various mechanisms involved in the development of tolerance in T and B lymphocytes to understand the causes of immunodeficiences, malignancies and autoimmunity so that therapies can be developed; development of improved methods of immune therapy against infections through the manipulation of genes encoding for receptors; development of procedures to introduce human genes into animals in order to prepare monoclonal antibodies against specific human antigens; studies on genes and cell membrane molecules involved in lymphocyte activation to help in the design of immunoenhancing and immunosuppressive drugs. In addition, a program to acquire and distribute monoclonal antibodies should be developed so that they can be used to selectively attack subsets of human lymphocytes, thereby permitting research to understand the immune system functions and to treat immune system disorders. Referral centers should be set up around the country to concentrate multidisciplinary research efforts for the small number of children who suffer from childhood immunodeficiences.

TRANSPLANTATION: Studies are needed on methods of tolerance induction to aid in development of procedures to minimize the immune response to organ grafts. In addition, monoclonal antibodies against antigens unique to specific organs should be developed which can be used for specific immunosuppression in organ transplant recipients. Mouse models should also be developed in which monoclonal antibodies against histocompatibility antigens can be produced to provide information applicable to use of this approach in humans. A major effort is needed on the purification of class I and class II major histocompatibility complex molecules. A better understanding of how these molecules control susceptibillity to disease and how they initiate transplantation rejection would be helpful to improving transplantation procedures.

MAJOR NEW CLINICAL TRIALS: The following clinical trials are ready to begin: 1) efficacy of recombinant DNA hepatitis B vaccines; 2) efficacy of DHPG to prevent cytomegalovirus infection in bone marrow transplant patients; 3) expanded trials of recombinant DNA malaria vaccines; 4) efficacy of live, attenuated hepatitis A virus vaccine; 5) efficacy of monoclonal antibodies in preventing rejection in bone marrow transplantation; and 6) comparison of experimental therapy regimens for systemic candidiasis.

OUTREACH: Outreach efforts should be initiated in the areas of asthma, childhood immunodeficiencies, transplantation and adult immunization. In addition, a core outreach component should be added to each of NIAID's Centers for Interdisciplinary Research on Immunologic Diseases for the transfer of technology related to basic and clinical immunology.

Mr. **Early**. Doctor, I want to thank you for your testimony and I want to thank you for your contribution as Director.

I want to reiterate that the presentation of the charts was well done. As a layman I was able to follow it; and when I can follow it, it must be well explained.

Dr. **Fauci**. You are welcome. Thank you.

Mr. **Early**. The Subcommittee will adjourn.

[The following questions were submitted to be answered for the records:]

AIR-CONDITIONING EQUIPMENT MECHANIC

ADULT IMMUNIZATION

Mr. Conte. Yesterday we heard from Dr. Loe at the Dental Institute about a major initiative they're making to address oral diseases in the elderly. You and I talked last year about the host of possibilities for immunizing adults against disease. What vaccines can be given to adults, and are you doing anything to push the adult population to consider immunization?

Dr. Fauci. A number of vaccines are recommended for adults depending on the age, occupation, and health status of the individual. First consideration should be given to immunizing adults, particularly the current college-age generation, with those pediatric vaccines that were not available or not widely used when they were children. This would not include pertussis, but would include tetanus vaccine with a diminished component of diphtheria toxoid. Measles and rubella vaccines should be administered, the latter particularly to susceptible females to prevent the congenital rubella syndrome in their future offspring. Influenza and pneumococcal vaccines are recommended for specified high risk groups, particularly those with underlying cardiovascular disease and those over 65 years of age. A booster dose of poliovirus vaccine should be given to those traveling to endemic areas. Inactivated poliovirus should be given to parents not previously immunized before their children are given oral polio vaccine. Hepatitis B virus vaccine is recommended for dentists, surgeons, and other health professionals exposed to blood and body secretions and to those at high risk for other reasons. Rabies vaccine is recommended for veterinary students, veterinarians, foresters, and others at risk of exposure. Yellow fever vaccine is recommended for those traveling to endemic areas. NIAID has joined with other components of the Public Health Service and with private groups such as the American College of Physicians and the National Foundation for Infectious Diseases through press conferences, seminars, and workshops to inform both physicians and the public regarding the use of vaccines in adults.

TRANSPLANTATION

Mr. Conte. What advances have been made in the last year with regard to transplantation?

Dr. Fauci. In the past year, the most important research advance in transplantation has been the progress achieved in manipulating the immune system to reduce graft rejection. New combinations of immunosuppressive technologies, such as total lymphoid irradiation combined with anti-lymphocyte globulin administration, have been tested and found effective with and without cyclosporine. New monoclonal antibodies, prepared against functional subpopulations of lymphocytes, are being tested clinically; several show promise for the prevention of rejection. In addition to being used as modulators of immunocompetent cell populations, monoclonal antibodies are being employed to remove from donor bone marrow the specific cells capable of causing graft-versus-host disease.

Mr. Conte. Are there any new programs planned which will increase graft survival or expand the transplant population?

Dr. Fauci. Planned efforts for increasing the survival of transplanted tissues or organs and expanding the donor pool parallel the research priorities of the Task Force on Organ Transplantation. We have encouraged the submission of research applications for studies on the elucidation of the mechanism of action of cyclosporine, a widely used immunosuppressive drug, to determine procedures for optimizing the drug's immunosuppressive properties and reducing its deleterious effects. We also expect to support new program projects concerned with the various aspects of clinical transplantation, including immunosuppressive therapy and preservation of donor organs. Also, new efforts to obtain improved tissue-matching reagents for transplantation in minority populations are now under way.

IMMUNOMODULATORS

Mr. Conte. We've read some recently about several naturally occurring substances that regulate immune responses and are now being prepared in bulk amounts by new techniques of molecular biology. Some of these substances are, or are expected to be, of commercial importance. What are these substances and how will they be useful in the treatment of disease?

Dr. Fauci. I will discuss three of these substances with which we are reasonably well-acquainted at present. One of them is gamma interferon. When the interferons were discovered some years ago, they seemed to offer great promise in the treatment of viral diseases--a promise that has been partly realized. More recently, it has been learned that interferons affect immune responses, sometimes in a profound way. Gamma interferon is produced by stimulated T lymphocytes. Its effects on immune responses include activating certain naturally occurring "killer" cells that are capable of attacking some tumor cells and virus-infected cells. In addition, gamma interferon aids another substance known as interleukin-2 in promoting the growth of T lymphocytes and, thus, in the expansion and amplification of immune responses. Interleukins-1 and -2 both act on T-lymphocytes to expand and amplify immune responses and to enhance the aggressive functions of "killer" cells toward tumor cells, virus-infected cells, and certain parasites. Thus, all these substances--gamma interferon and the interleukins--play essential roles in promoting immune responses.

The genes for all three substances have been identified and isolated. Using recombinant DNA technology to transfer these genes into appropriate host cells, such as certain bacteria or yeasts, we have obtained large quantities of the substances. The availability of large quantities of the substances in pure form, which is a very recent accomplishment, permits the use of these substances in the treatment of diseases such as human cancers where there is already evidence that they may be effective. In addition, the availability of the substances allows exploration of their efficacy in treating other diseases, particularly those that involve immunological deficiency and derangement. Such investigations had not been possible previously owing to the shortage or impurity of the substances.

OUTREACH

Mr. Roybal. Your Institute has been very active in efforts to bring the latest biomedical research information to the public through technology transfer and outreach programs. Would you tell us about some of your accomplishments and your plans in outreach?

Dr. Fauci. Since 1984, the NIAID outreach and technology transfer program has conducted conferences on AIDS for primary care physicians, health care workers, and service personnel in eight U.S. cities with repeated conferences in Los Angeles and Washington, D.C. These conferences have been very well received. Another Washington, D.C. conference, which will emphasize AIDS in minorities, is planned for April 12, 1986. The outreach program also supported a conference on pediatric AIDS and partially supported the International Conference on AIDS in Atlanta in April 1985. The program has arranged for and supported travel of NIH staff to speak at professional and lay organization meetings and organized a workshop on AIDS for the 1985 meeting of the National Medical Association.

The outreach program has also supported conferences on systemic lupus erythematosus, childhood immunodeficiency, immune system disorders, organ transplantation, and the immune system and neurologic disorders in various U.S. cities.

Within the proposed allocation from OASH, we plan to maintain the outreach program for AIDS in FY 1987 at the 1986 level. We plan to sponsor conferences for health care providers and service personnel at a rate of one conference every 2 to 3 months. Outreach efforts in non-AIDS areas of the Institute's mission will be minimal and conducted through our CIRIDs program to the extent possible.

CIRIDs

Mr. Roybal. We understand that, in response to our request, the CIRID Directors met to discuss outreach efforts. Would you inform us of the outcome of that meeting and describe what recommendations have resulted from that meeting?

Dr. Fauci. In response to your request, NIAID held a meeting of the CIRID Directors on December 11, 1985. The recommendations resulting from the meeting follow:

1) Establish a "core" outreach/demonstration component in each CIRID for education of health care practitioners and the public.

2) Develop collaborative efforts among the CIRIDs to:

    a. Implement Self Management of Asthma Programs.
    b. Develop AIDS community resource publications.
    c. Develop collaborations on other specific disorders.

3) Convene periodic meetings of CIRID Directors along with AADC Directors to implement specific community programs.

Efforts will be made to implement these recommendations to the extent possible within available funding.

Mr. Roybal. What specific educational and outreach programs have been developed for AIDS through the CIRID programs?

Dr. Fauci. The CIRIDs at the University of California in Los Angeles, Georgetown University, and Boston Children's Hospital have held meetings in their communities for health practitioners and lay people in an effort to provide current information and future perspectives on AIDS. In 1982, 1983, and 1984, these programs were started in Los Angeles, Washington, D.C., and Boston, respectively, and have been repeated since then. Generally, the programs consisted of a one-day meeting for physicians and health care providers, followed by another one-day session for the concerned public. Intervention programs for physicians have been developed at UCLA and Georgetown to offer the practitioner community educational materials and other information.

The UCLA CIRID has developed a regional resource reference guide for health professionals, containing information about medical, diagnostic, treatment, and prevention aspects of AIDS. It also provides a complete listing of community resources for AIDS victims, identifying available social services and legal assistance. The publication will be distributed for the second time in the Los Angeles area. The NIAID also is cooperating with the Georgetown CIRID to develop a similar reference resource guide for the Washington area; if resources are available, this guide will be published in other regions.

Mr. Roybal. What research projects in the CIRID programs are directed at developing a vaccine against H. influenzae, a leading cause of death and morbidity in infants?

Dr. Fauci. The CIRID at Georgetown University has been attempting to develop a live vaccine for the prevention of infection by Haemophilus influenzae, which causes meningitis, fatal epiglottitis, obstructive bronchiolitis, otitis media, septic arthritis, laryngitis, cellulitis, and pneumonia in children and adults. In the United States, there are approximately 10,000 annual cases of meningitis resulting from this bacterium. Rapid diagnosis and treatment with ampicillin or chloramphenicol usually leads to recovery, although there is a mortality rate of 5 to 10 percent, and a number of patients who do recover suffer permanent neurologic damage. However, the recent emergence of antibiotic resistance in this organism has complicated therapy.

The existence of antibiotic-resistant H. influenzae and the high incidence of serious permanent neurologic complications in infected individuals underscores the need for a vaccine to prevent infection. The Georgetown CIRID investigators have prepared and characterized temperature-sensitive mutant strains of H. influenzae, and their immunizing potential is being evaluated.

Mr. Roybal. What research programs have been developed through the CIRID programs in the area of risk reduction in the allergic and immunologic diseases; e.g., AIDS, and self-management programs in childhood asthma?

Dr. Fauci. All CIRIDs are actively involved in outreach programs for practicing physicians and the public. These programs emphasize medical up-dates for physicians and provide patients, their families, and the concerned public with useful information about allergic and immunologic diseases.

In addition, more focused educational programs concerned with self-management and risk reduction also have been developed and are being instituted at every CIRID. The most established program of this type is the Asthma Care Treatment (ACT) program developed at the UCLA CIRID specifically for self-management of asthma in children. This program has been quite successful; children in the program have learned to control their disease quite effectively as evidenced by reduced hospitalizations, physician visits, and school absenteeism. A similar ACT program for Hispanic children, with instructional materials in Spanish, is now being developed at the UCLA CIRID. This ACT program also is being used at the Washington University CIRID, and a modified version is in use at the Georgetown CIRID. The Johns Hopkins and Boston Children's CIRIDs are developing similar programs. Plans have been developed to make the ACT program available nationwide in collaboration with the Asthma and Allergy Foundation of America and with support from a pharmaceutical manufacturer.

Similar efforts concerning AIDS are under way. At the UCLA CIRID, a regional resource reference guide for health-care professionals and AIDS patients has been prepared and distributed, and educational programs for physicians and patients have been developed. The program for primary care physicians is designed to inform them of current advances in diagnosis, treatment, and prevention and to enhance their ability to counsel patients and individuals at risk on methods and approaches for risk reduction. The Georgetown CIRID also has developed educational programs and is preparing a similar reference guide in collaboration with the NIAID. If resources permit, plans to make this guide available in other regions will be implemented.

Mr. Roybal. What associated research projects have been developed through the CIRID programs such as work on co-pathogens or fundamental mechanisms of immune regulation that can be identified as increasing our understanding of the AIDS virus and its infectivity?

Dr. Fauci. Although HTLV-III is accepted as the causative agent of AIDS, it is not yet clear why only some individuals who have been exposed to this virus actually develop AIDS. There is reason to believe that other factors may influence the occurrence of AIDS; certainly, many AIDS patients have an extensive medical history of other sexually transmitted diseases, hepatitis, and other infections.

The CIRIDs at the University of California in Los Angeles and at Georgetown University are actively involved in studies of possible co-factors or co-pathogens in AIDS. The UCLA group has access to a large population of individuals at risk who are part of a study on the natural history of AIDS. These individuals have been evaluated extensively on entry to the study, and careful follow-up studies are now in progress. Preliminary results from a small number of AIDS patients in this study group suggest that the cytomegalovirus (CMV) may be a significant co-pathogen. It appears that after initial infection with HTLV-III, these patients experienced frequent CMV reinfections; they exhibited very high levels of antibody against CMV when AIDS became clinically evident. The Georgetown CIRID is examining the possibility that frequent infections with CMV lead to the development of a progressive impairment of cell-mediated immune responses which predisposes the AIDS patient to a spectrum of opportunistic infections and malignancy, particularly Kaposi's sarcoma.

AIDS

Mr. Roybal. What progress has been made in the development of a vaccine against AIDS?

Dr. Fauci. Many different approaches to develop AIDS vaccines are being explored. These include the use of purified viral proteins from native viral material or infected cells, the generation of recombinant vaccinia viruses that contain the antigens of HTLV-III/LAV, the expression of the antigens of HTLV-III/LAV in bacteria or other expression systems, the use of anti-idiotype antibodies, and the use of other vectors, such as attenuated herpes simplex or attenuated cytomegalovirus to introduce the necessary antigens. All these approaches have advantages and disadvantages. It is necessary to look at each carefully and evaluate its potential.

Mr. Roybal. What assurances have you been given by the Assistant Secretary that the $67,731,000 you have earmarked for AIDS will in fact be allocated to your Institute?

Dr. Fauci. The current anticipated reimbursement to the NIAID is now estimated at $67,520,000. We have been assured that, barring a dramatic change in requirements, brought about by unexpected developments in this disease, the planned amount will be readily available.

INFLUENZA

Mr. Roybal. What progress has been made in the treatment, prevention and diagnosis of respiratory infections, primarily influenza and pneumonia?

Dr. Fauci. Prevention and control of influenza virus infections have been major goals within the Institute since the early 1970's. NIAID-supported research has provided us with an understanding of the epidemiology of the disease and a biochemical and biophysical characterization of the virus itself. Strategies for vaccine development have resulted in the generation of an attenuated, live influenza vaccine. During the past 7 years, the live vaccine has been investigated in small clinical studies and has been shown to be safe (non-reactogenic), genetically stable, and capable of producing protective antibodies in recipients. The premise for this approach to vaccine development is that a live attenuated product will produce immunity of a longer duration and be very similar to that following natural infection. This promising product is administered as nose drops. Last year, the NIAID initiated a large comparative field trial of the live vaccine, inactivated vaccine, and placebo in normal children and adults at

Vanderbilt University. Results from this definitive trial should be available in 1990.

Antiviral drug development for prophylaxis of influenza has been highly successful. Amantadine is licensed for prophylactic use. It is also beneficial when used for treatment of uncomplicated influenzal disease. An analogue of amantadine, a drug called rimantadine, is currently undergoing clinical evaluation. Rimantadine is highly efficacious in preventing influenza infections and does not exhibit the side effects associated with amantadine (e.g., nervousness, inability to concentrate). Studies are now under way to assess the therapeutic usefulness of rimantadine in complicated influenza and influenza in the elderly.

The potential for expanding the armamentarium for combat of influenza is great. Experimentation currently in progress should provide us with many of the answers we have been seeking for the past 10 years.

Drug therapy for severe lower respiratory disease (LRI, bronchiolitis, pneumonia) in infants has taken a large step forward in recent years. Ribavirin has been ascertained to be effective therapeutically for LRI caused by respiratory syncytial virus (RSV), the major etiologic agent of LRI, and has been licensed by the FDA for this indication.

RSV vaccine development has been a slow and arduous task. Grantees and intramural scientists of the NIAID have successfully characterized the genome of the virus (i.e., cloned and sequenced), and studies are in progress to correlate antigenic structure and function. Vaccine candidates prepared from purified viral components should be forthcoming in the next several years. Work with RSV is taking great advantage of recombinant DNA technology and monoclonal antibody techniques.

A new vaccine for the prevention of bacteremic and non-bacteremic infection from Streptococcus pneumoniae has been licensed and is available. Like the previous pneumococcal vaccine, the new vaccine is composed of purified capsular pneumococcal antigens. The new vaccine is different from the previously available vaccine in two respects: 1) it contains antigens to 23 serotypes of pneumococcus, compared to antigens to the 14 serotypes in the previous formulation, and 2) the dose of each antigen in the vaccine has been reduced from 50 ug to 25 ug. The 23 serotypes in the new vaccine account for approximately 85-90 percent of bacteremic pneumococcal disease in the United States and in several other countries. In addition, the vaccine may provide some cross protection against other types of pneumococci that are not included in the vaccine but are related immunologically to types that are in the vaccine.

The NIAID continues to support a pneumococcal polysaccharide reference laboratory to study the effects of pneumococcal vaccine in patients with conditions predisposing to pneumococcal infections. The advent of the new polyvalent pneumococcal vaccine has expanded studies on the immune response of high risk patients to the vaccine, with special emphasis on the amount of antibody required for protection and its persistence. When the polysaccharide antigens of pneumococci are given to infants, no significant lasting protective effect is noted from the serotypes that cause most pneumococcal disease in this age group. It has been observed that the very capsular types that cause most of the pneumococcal disease in infants are the types that are the least immunogenic.

The solution to this problem may be to conjugate the polysaccharide antigens of the pneumococcus with a protein. This has been shown to improve the immunogenicity of other polysaccharide antigens. Conjugation of pneumococcal polysaccharide type 6A has been accomplished with tetanus toxoid, and has been tested in monkeys and human adults. Initial experiments showed that the conjugate vaccine induced higher seroconversion rates than polysaccharides alone. A field trial has yet to be done.

Effective conjugation of important serotypes could lead to the development of a pediatric vaccine effective against pneumococcal otitis media and pneumococcal pneumonia. Ideally, this would be given with DPT vaccine, before the age of 6 months. Such a vaccine might consist of tetanus toxoid or diphtheria toxoid conjugates of the six or so pneumococcal serotypes that cause most pediatric disease. This vaccine might also include conjugates of meningococcus and H. influenzae type b. Given at an early age, this vaccine could protect infants when the burden of disease is greatest.

Work is now in progress to develop better and more reliable tests for diagnosing pneumococcal disease that do not depend upon culture assays. This improved technology could greatly enhance the ability of clinicians to properly diagnose pneumococcal pneumonia and bacteremia in a very rapid fashion.

ALZHEIMER'S DISEASE

Mr. Roybal. Please describe what research is currently being undertaken pertaining to viral infections in Alzheimer's disease. What progress has been made to date? Do you plan to fund any research in the area in 1987?

Dr. Fauci. We are not funding any research directly on viral infections in Alzheimers' disease at the present time. We have solicited applications for research in this area, but there has been no positive response to this solicitation. However, we are funding research projects on model systems that could lead to information on how viruses could cause neural damage similar to Alzheimer's. These include studies on slow virus infections, viral persistence, and the relation of viruses to the genesis of chronic disease. These efforts will continue in FY 1987.

SEXUALLY TRANSMITTED DISEASES

Mr. Roybal. Last year you supplied this Committee with a table showing research dollars for each of the major sexually transmitted diseases and the amount of research for them over the last 5 years. Could you please update this table and again make it available to this Committee?

Dr. Fauci. NIAID obligations during the last 5 years for research on what are perhaps the four most significant sexually transmitted diseases follow:

(Dollars in thousands)

	FY 1981	FY 1982	FY 1983	FY 1984	FY 1985
Gonorrhea	$4,205	$3,431	$4,196	$4,753	$5,463
Chlamydial infections	1,482	1,342	1,619	2,422	3,726
Syphilis	967	1,453	1,762	1,798	2,063
Genital herpes	3,242	4,182	5,022	4,170	6,388

Mr. Roybal. What progress has been made in the treatment of chlamydia?

Dr. Fauci. The antibiotics tetracyline and erythromycin are still the preferred treatment for chlamydial infections. Other antibiotics such as rifampicin, doxycycline, and ampicillin are also effective but are fraught with the problem of developing resistance to the drugs.

Mr. Roybal. How close are we to developing an inexpensive diagnostic test and treatment?

Dr. Fauci. A rapid, specific diagnostic test for chlamydial infections was developed 2 years ago through combined Federal and commercial support. Test kits are now available commercially at a relatively inexpensive cost. Distribution and training in the use of these kits in the hands of the clinician and clinical laboratory personnel have been initiated. Once diagnosis is made, effective treatment is readily available.

GRAMM-RUDMAN REDUCTIONS

Mr. Stokes. Dr. Fauci, your FY 1987 budget request seeks to restore the 1986 Gramm-Rudman reductions in your Institute's intramural program while funding for the other research programs is projected to decrease. Why is that?

Dr. Fauci. The 1987 request for the intramural program reflects the revised 1986 base with only partial funding of the administrative mandatory increases for FY 1987 including increased costs for central services. Starting in 1983, intramural staff have been increasingly directed to work on AIDS. The decision was made not to reduce intramural funding below the 1986 level so that we might preserve the non-AIDS efforts.

Mr. Stokes. Dr. Fauci, what areas of research will be affected by the 1986 Gramm-Rudman reduction of $16.488 million for your Institute?

Dr. Fauci. The sequestration was applied to all budget mechanisms and therefore will affect all the research activities of this Institute, including basic and clinical studies on immune system disorders, sexually transmitted diseases, vaccine development and testing, antiviral drug development and testing, transplantation immunology, and tropical diseases.

Mr. Stokes. Do you anticipate requesting any reprogramming in order to protect any high priority research activities from Gramm-Rudman reductions?

Dr. Fauci. We are reviewing our programs at this time and will forward reprogramming requests, if needed.

OUTREACH FOR MINORITIES

Mr. Stokes. Dr. Fauci, one in four AIDS victims is black. What outreach/technology transfer activities conducted by your Institute have been aimed at minority physicians and health care workers and minority organizations?

Dr. Fauci. We have taken steps to increase the awareness of AIDS through conferences directed to minority audiences. One of these will be held in Washington, D.C., on April 12, 1986. Through conferences such as these, we hope to be able to educate minority professionals and professionals caring for minorities with AIDS. In addition, we have taken every opportunity available to us to speak to minority organizations about AIDS. The National Medical Association has been particularly useful in helping us reach minority phyisicians and nurses regarding this important problem.

RESEARCH AREAS SUFFERING BECAUSE OF AIDS

Mr. Stokes. Dr. Fauci, your budget justification states that "since the recognition of AIDS in 1981, the NIAID's Intramural Research Program has steadily increased its basic and clinical research on this disease and has been responsible for the precise delineation of the immune defect that is characteristic of the disease. In recognition of the need for increased extramural effort, the NIAID established an Acquired Immunodeficiency Syndrome Program..." My question is have any research areas within your Institute suffered because of all the emphasis placed on AIDS research?

Dr. Fauci. The Institute has been redirecting resources into AIDS since FY 1982. The redirection of effort to AIDS has impacted upon, to varying degrees, all the research areas supported by the Institute. It should be noted, however, that what we learn from our research on AIDS may have an impact on studies of other viruses which may cause deficiencies of the immune system. In addition, we are learning about the internal workings of the immune system as a result of this research.

Mr. Stokes. What research areas, other than AIDS, are we presently giving inadequate attention?

Dr. Fauci. Those research areas that have received reduced attention particularly as a result of redirected personnel resources include the following: hepatitis, slow virus diseases, basic molecular biology, immunoregulation, immune disorders, mucosal immunity, parasitic diseases, sexually transmitted diseases, epidemiology on Lyme disease and enteric diseases, antivirals for influenza, genital herpes, gential warts, encephalitis, influenza and other respiratory viral diseases.

REDUCTIONS IN RESEARCH CENTERS

Mr. Stokes. The budget justification indicates that the number of research centers funded by your Institute will drop from 18 to 14 in FY 1987. The justification further states that "no competing centers will be funded." What is the rationale for this?

Dr. Fauci. Within the funds available in the FY 1987 budget, an attempt was made to maintain balance between investigator-initiated research and more targeted or applied research. Since 70 percent of the Institute's budget was directed to investigator-initiated research project grants, the centers category was necessarily reduced to a significant degree.

Mr. Stokes. Dr. Fauci, do you believe that the research being conducted in the four centers which will not be renewed is of high scientific merit?

Dr. Fauci. Yes, the research being conducted in these four centers is of high scientific merit.

Mr. Stokes. Dr. Fauci, are you comfortable with the fact that support for the remaining centers will be reduced by an average of 30 percent in FY 1987 in addition to a 7 percent reduction in 1986?

Dr. Fauci. Hard choices had to be made and this was one of them.

Mr. Stokes. What impact will a reduction of this magnitude have on the research activities conducted by the centers?

Dr. Fauci. Research activities at these centers are expected to be affected. This funding reduction will necessitate either a reduction in research and support personnel or a reduction in other operating costs such as equipment, materials, and supplies. Either choice made by the center directors will reduce the pace of research activity, knowledge acquisition, and application of research findings to clinical problems. The reduced funding could result in medical scientists who are now committed to research in allergic and immunologic diseases to seek other means of support and lead them to other areas, if not away from, scientific inquiry.

REDUCTION IN RESEARCH TRAINING

Mr. Stokes. The number of individual and institutional training awards for your institute is scheduled to drop from 491 awards under the 1986 appropriation to 375 awards under the FY 1987 budget request. That is a reduction of almost 25 percent. How will the reduced training awards affect your efforts to expand training opportunities for minority scientists?

Dr. Fauci. The reductions proposed for FY 1987 will not allow the Institute to fund as many awards as are projected for the current fiscal year. However, the overall reductions alone will not result in commensurate reductions in all categories of fellows and trainees. The Institute will make every attempt to fulfill its mission with respect to training in priority areas, while at the same time increasing the number of training opportunities for minority scientists. Meharry Medical College recently received two training grants that have been approved for support for the remainder of this decade. Under one of these, three predoctorals and two postdoctorals will be trained per year. Under the other, five health professional students per year also will experience the activities and excitement associated with a career in science. Over the next 5 years, these trainees will represent new additions to the pool of minority biomedical scientists.

Special efforts are being made this year to communicate to as large a minority audience as possible the availability of NIAID training programs. Efforts to communicate to large audiences are now being complemented by follow up, small workshops with interested students and faculty. Data regarding the number of funded training grants in a discrete area of science are provided as are the names and addresses of principal investigators, project titles, number of approved training positions and duration of the award. It is expected that these proactive and tailored efforts will result in increasing the number of minorities being trained under NIAID-sponsored programs.

INCREASED MINORITIES IN TRAINING

Mr. Stokes. What is your institute doing to increase the number of minorities supported through institutional training grants that go to nonminority institutions?

Dr. Fauci. Program Directors of NIAID-supported Institutional National Research Service Awards (NRSA) are encouraged to recruit under-represented minorities for appointment to their training programs. Also, the Institute now requests that NRSA Program

Directors include information in their annual progress reports regarding recruitment efforts targeted to minority groups. During review of all competitive renewal applications, Institute staff, as well as members of the Initial Review Groups and our National Advisory Council, pay special attention to each competing program's record in the recruitment and retention of minorities.

Additional Institute efforts include sponsoring exhibits at, and sending Institute representatives to, national scientific meetings that attract large minority audiences. Institute staff also make presentations and discuss training opportunities at numerous regional workshops. Also, information is disseminated to targeted audiences regarding available training opportunities by geographic location, scientific discipline, number of training slots available, etc.

AWARDS TO HISTORICALLY BLACK COLLEGES

Mr. Stokes. In 1984, your institute awarded $341,713 in research grants to historically black colleges. How much was awarded in 1985? What are your goals for 1986 and 1987?

Dr. Fauci. Support to historically black colleges totalled $494,196 in FY 1985. Estimated support in FY 1986 and FY 1987 is $494,000 and $480,000, respectively.

RESEARCH OPPORTUNITIES FOR MINORITIES

Mr. Stokes. Please update the table on page 161 of last year's hearing record regarding research opportunities for minorities.

Dr. Fauci. Estimated support for our programs that encourage minority participation in biomedical research in fiscal years 1986 and 1987 is as follows:

	1986 Estimate	1987 Estimate
Minority Biomedical Support (MBS)	$440,000	$460,000
Minority Access to Research Careers (MARC)	25,000	25,000
An Introduction to Biomedical Research	35,000	35,000
Minority Research Enhancement Program	75,000	50,000

EEO GOALS

Mr. Stokes. Dr. Fauci, do you establish goals for your senior administrators for addressing minority program and personnel issues? If not, why not?

Dr. Fauci. Our overall goal in NIAID is affirmative action and equal employment opportunity for all people. Each NIAID senior administrator in the Senior Executive Service (SES) or Performance Management and Recognition System (PMRS) must develop a performance plan at the beginning of each fiscal year. We require that one element in the plan relate to equal employment opportunity.

Mr. Stokes. How do you hold your senior officers accountable for meeting those goals?

Dr. Fauci. At the end of each fiscal year, each SES and PMRS employee is rated by his supervisor as to his actual achievements in meeting each of the elements in the performance plan, including the EEO element. The pay received by the employee is tied to the overall rating he receives.

Mr. Stokes. Please supply for the record the following information for SES, senior level administrative and senior level professional positions: the current number of all such positions and the current number of these positions occupied by blacks.

Dr. Fauci. The NIAID has eleven SES positions. Eight of these are in the intramural Senior Scientific Service. Of the remaining three, one position is held by a black male, who is the Director of our Extramural Activities Program.

EEO OFFICER

Mr. Stokes. I understand that the equal employment officer for your Institute is currently on detail for a year to another agency. If this is correct, who is currently performing his responsibilities?

Dr. Fauci. Mr. Franklin Fountain, EEO Officer, NIAID, is not on detail to another agency but rather to the NIAID Extramural Activities Program. Mr. Vincent A. Thomas, Jr., NIAID Management Analysis Officer, is serving as Acting EEO Officer. He is ably qualified for the acting position since he served as the NIAID EEO Officer for several years in the past.

Mr. Stokes. How can you assure me that EEO activities will be given sufficient priority during the period while the permanent EEO officer is on detail?

Dr. Fauci. My senior staff know of and understand my commitment to the Affirmative Action and Equal Employment Opportunity Program. They will assist Mr. Thomas in keeping this program vital.

RESCISSION

Mr. Early. Yesterday in answer to one of my questions I was told the amount of the rescission being proposed for one of the institutes had been "assigned" to that institute. Doctor, what I'd like to know is, how were the institutes selected for a rescission (some institutes do not have rescissions), and how were the amounts of the rescissions for the various institutes arrived at?

Dr. Fauci. While the total amount of the rescission for research project grants was mandated by OMB, the Office of the Director, NIH had responsibility for allocation of the total among the Institutes. The amount was determined in two steps: 1) simple proration; 2) then the prorated amounts were adjusted to reflect NIH scientific priorities and research opportunities.

Mr. Early. In your professional judgment, overall what kind of an impact would this rescission ($1.513 million), in addition to the $16.488 million sequestered, have on your programs in FY 1986?

Dr. Fauci. In my professional judgement the impact of the rescission will be felt in the reduced payline and number of competing research project grants NIAID will be able to fund. This will require that only exceptionally high priority investigator-initiated research be supported.

RESEARCH CENTERS

Mr. Early. How many centers will be up for renewal in FY 1987? Provide the names and location of these for the record.

Dr. Fauci. Four Asthma and Allergic Diseases Centers will be up for renewal in FY 1987:

Asthma and Allergic Disease Center Program Grant,
  Mayo Clinic and Foundation, Rochester, Minnesota
Pathogenesis of Urticaria, Angioedema and Vasculitis,
  State University of New York at Stony Brook, New York
Immunoregulation in Allergic/Hypersensitivity Disease,
  Tufts University School of Medicine, Boston, Massachusetts
Allergy and Clinical Immunology Program, The Rockefeller
  University and Cornell University, New York, New York

CLINICAL TRIALS

Mr. Early. How many new clinical trials were started during FY 1986? If any new ones will be started, please provide a list.

Dr. Fauci. During FY 1986, only one new trial is expected to be initiated, an acellular pertussis vaccine trial in Sweden.

Mr. Early. How many clinical trials are under way in FY 1986? Provide a list of the clinical trials which will be under way in FY 1986, and indicate their associated cost.

Dr. Fauci. There are 69 clinical trials under way in FY 1986. A listing of these trials, together with the estimated funding for each, follows:

Title	1986 Estimate
A Study of Allergy to Ragweed Pollen	$197,000
Interferon, Immunity and Latent Viruses	160,000
An *in vitro* Approach to Problems of Clinical Allergy	211,000
Chemistry and Immunology of Streptococcal M Proteins	23,000
Lethal Bacteremia	209,000
Experimental and Clinical Allograft Unresponsiveness	79,000
Immune Regulation in Visceral Leishmaniasis	26,000
Antischistosomal Drugs Efficacy and Toxicology	26,000
Study of Antischistosomal Drugs	26,000
Human Filariasis in Colombia	30,000
Filariasis in Haiti	30,000
Prevention of Cytomegalovirus Infections	34,000
H. influenzae b and *S. pneumoniae* Carbohydrate Vaccines	26,000
Genetic Control of Antibody Responses to Polysaccharides	116,000
Prevention of Infections with a Bacterial Polysaccharide Immunoglobulin	62,000
Nosocomial Infections in Surgical Patients	28,000
Clinical Epidemiology - Pathogenesis of Genital Herpes	70,000
Cellular Immunology and Responses by Lymphokines	49,000
Clinical Studies of Kaposi's Sarcoma and Related AIDS	196,000
Prevalence and Pathogenesis of Cryptosporidiosis	35,000
Prophylaxis of *H. influenzae* and Other Infections	269,000
Immunotherapy of Childhood Asthma	162,000
Role and Effect of Gamma Interferon in AIDS	44,000
Allergens of *Aspergillus fumigatus*	14,000
Gamma Interferon--*Mycobacterium avium* Infection in AIDS	29,000
Immunotherapy for Adult Asthmatics (Sensitive to Ragweed)	447,000
Immunotherapy for Adult Asthmatics (Sensitive to House Dust Mites)	642,000
Polymerized Allergens	80,000
Immunotherapy in Cat-Induced Asthma	47,000
Complement Pathways in Normal and Disease States	14,000
Suboptimal Immunotherapy for Aero-Allergen Disease	45,000
Clinical Evaluation of Live Herpesvirus Vaccine	211,000
Pneumococcal Polysaccharide Reference Laboratory	158,000
Infectious Enteric Disease Studies	289,000
Study of Vaccines for Infectious Diseases	509,000
Efficacy Trials of Antivirals for Severe Herpesvirus	971,000
Clinical Trials for Evaluation of Antivirals	334,000
Treatment of Juvenile Laryngeal Papilloma with Interferon	105,000
Evaluate Control Measures Against Infectious Diseases	319,000
Treatment of Condyloma Acuminatum With Interferon	306,000
H. influenzae type b Vaccine in High Risk Infants	638,000
Testing of An Acellular *Bordetella pertussis* Vaccine	51,000
Evaluation of Live Attenuated and Inactivated Influenza Vaccines	560,000
Multicenter Study of Prevention of Prematurity by Detection and Treatment of Gestational Genitourinary Infections	550,000
Clinical Trials for Therapy of Systemic Mycotic Diseases	266,000
Testing of Respiratory, Enteric and Bacterial Vaccines	1,391,000
Monoclonal Antibody Treatment of Kidney Graft Rejection	1,047,000
Evaluation of the Role of Immunotherapy in the Treatment of Laboratory Animal Allergy	262,000
Rimantadine or Amantadine in the Treatment of Influenza	641,000
Efficacy Trial of Cold-Adapted Vaccines	396,000

Clinical Trial of Prophylaxis of Anaphylactoid Reactions to Radio Contrast Media	129,000
Trial for Prophylaxis of P. carinii among AIDS Patients	503,000
Studies on the Antigens of Group B Streptococcus	11,000
Acellular Pertussis Vaccine Trial in Sweden	220,000
Treatment of Disease with the Interferon System	46,000
Immunology and Chemotherapy of Systemic Mycoses	198,000
Studies on Patients with Known/Suspected Parasitic Diseases	72,000
Pathogenesis/Chemotherapy of Herpesvirus Infections in Man	344,000
Pathogenesis of Infection with Intracellular Parasites	9,000
Phagocytic Cell Function	624,000
Clinical, Immunopathogenic, and Therapeutic Studies in the Spectrum of Vasculitis	146,000
Mast Cell Dysfunction in Systemic Mast Cell Disorders	57,000
Inflammatory Disorders of the Gastrointestinal Tract	20,000
Evaluation of Hepatitis B Vaccines	33,000
Evaluation of Respiratory Viruses in Volunteers	197,000
Studies of Rotaviruses in Volunteers	355,000
Clinical and Therapeutic Studies in Human Filariasis	49,000
Rotavirus Vaccine Trial in Umea, Sweden	43,000
Rotavirus Vaccine Field Trial in Venezuela	43,000
Total	15,529,000

Mr. Early. Will you have to curtail any ongoing clinical trials with your FY 1986 revised budget request? If so, which ones?

Dr. Fauci. Ongoing clinical trials will not be curtailed under the revised FY 1986 budget.

Mr. Early. Doctor, will you have to curtail any ongoing clinical trials with your FY 1987 budget request? If so, which ones?

Dr. Fauci. Under the FY 1987 request, a clinical trial of rotavirus vaccines and the data-coordinating center for collaborative clinical trials of therapies for systemic mycotic disease will be terminated.

Mr. Early. Will you be able to start any new clinical trials in FY 1987?

Dr. Fauci. No major new clinical trials will be started in FY 1987.

CLINICAL TRIALS UNABLE TO FUND

Mr. Early. Are there any high priority clinical trials which are ready but cannot be initiated because of lack of funds in the FY 1987 request? If so, please provide a list of these, along with a brief description and the associated costs, including first year costs.

Dr. Fauci. The information follows:

HIGH PRIORITY CLINICAL TRIALS
READY TO BEGIN BUT FOR WHICH
FUNDING IS NOT AVAILABLE WITHIN THE FY 1987 BUDGET

1. Monoclonal Antibodies in Bone Marrow Transplantation

Immunodeficiencies, both acquired and congenital, have considerable medical and socioeconomic impact on the U.S. population. Congenital immunodeficiency is the result of a genetic defect in cell populations within the immune system preventing the proper function of the affected cells. The most marked form is Severe Combined Immunodeficiency (SCID). Mortality results from the complications of increased susceptibility to infection. At present the only known treatment for this condition is immunologic reconstitution. Allogeneic bone marrow transplantation has shown increasing success in immunodeficient patients.

Bone marrow transplantation is the treatment of choice for the acute form of leukemia which causes approximately 55 percent of leukemia deaths and compromises roughly one-half of all neoplasms in children. Half of the annual 1,000 new cases of aplastic anemia are candidates for bone marrow transplants. It is also being used, on an experimental basis, as a treatment for AIDS. In addition, it has been used to correct thallasemia and is a possible treatment for certain enzyme deficiencies.

The use of monoclonal antibodies to facilitate engraftment of bone marrow and to reduce instances of graft-versus-host disease has been shown to be effective in a number of isolated trials. A coordinated effort is now needed to identify the most effective antibody types and to design the optimal protocols.

Duration:	4 years
First Year Cost:	$1,200,000
Total Cost:	$4,800,000

2. Efficacy Trial for rDNA Hepatitis B Vaccines

About 200,000 cases of Type B viral hepatitis (HBV) are estimated to occur yearly in the United States, 10 percent of which develop into chronic carriers. A high percentage of these chronic cases progress to cirrhosis and eventually may go on to death from primary hepatocellular carcinomas (PHC). Currently, there are at least 800,000 chronic carriers in the United States and 200 million worldwide. Perinatal transmission accounts for 75 percent of the worldwide chronic cases. The estimated cost of HBV infection, chronic disease development, and PHC is about $250,000,000 per year in the United States alone. At present, licensed HBV vaccines are prepared from the plasma of human chronic carriers and preparation procedures are complex and time consuming. Using rDNA techniques, new protein coding areas of the HBV genome were identified. One such is the pre-S region, which is adjacent to the HBsAG coding sequences. Recent data indicate that pre-S enhances the immune response (IR) to HBsAG and that the earliest IR is to pre-S itself. Since the preparation process for plasma-derived vaccines removes this region, the possibility exists that rDNA vaccines containing both pre-S and S will provide better protection against perinatal transmission. Testing of vaccines having S alone and S plus pre-S could be performed within a 4-year timeframe. Corporations are interested in participating in the trial. Such an efficacy trial is best done with an at-risk population to whom vaccine is not available. This type of population exists in the Peoples Republic of China (PRC). Data indicate that about 4 percent of the mothers in the previously utilized locales are chronic carriers (about 110 infants per year). Anywhere from 50 to 70 percent of their infants will develop infection. In the past the NIAID and the CDC have worked together with the PRC under the U.S.-China Bilateral Science Agreement to test the NIAID-developed hepatitis B vaccine.

Duration:	4 years
First Year Cost:	$150,000
Total Cost:	$600,000

3. DHPG Prophylaxis of CMV in Bone Marrow Transplant Patients

Approximately 1,000 bone marrow transplants are done in North America each year. Cytomegalovirus (CMV) pneumonia is one of the leading causes of mortality in such patients, accounting for 10-20 percent of deaths in all bone marrow transplant patients. The syndrome carries a case fatality rate of 60 to 90 percent.

Data show that treatment of CMV pneumonia, once the pneumonia is clinically apparent, is too late. It is possible that the incidence of CMV pneumonia could be reduced or eliminated if patients were on long-term antiviral suppressive therapy with DHPG during the high-risk period following a bone marrow transplant. Approximately 300 patients have been treated with DHPG to date, all on compassionate drug use. All patients have had an underlying immunodeficiency and documented CMV infection, which was considered to be either life- or sight-threatening. Sufficient pharmacokinetic data are available to make accurate decisions regarding dose levels and plasma levels.

Because of the low patient number of CMV in bone marrow transplants, it is unlikely that a pharmaceutical company would be willing to fund this study solely for the purpose of gaining an additional indication for an "orphan" drug such as DHPG.

Duration:	2 years
First Year Cost:	$450,000
Total Cost:	$900,000

4. Expanded Phase I and II Trials of Antimalarial Vaccines

Malaria remains one of the world's most serious health problems in terms of both mortality and morbidity. Even for U.S. citizens, the danger of acquiring malaria during travel abroad and as an actual and potential health risk for our military forces is a matter of growing importance. Because of increasing drug resistance of the malaria parasite, plus increasing insecticide resistance of the mosquito vector, the measures for controlling and treating malaria continue to dwindle. Therefore, the need for new and more effective measures to control and treat malaria assumes greater significance. The new biotechnology has opened new approaches to develop candidate vaccines. NIAID scientists are already involved in a collaborative project with investigators at Walter Reed Army Institute of Research (WRAIR) with proposed Phase I (hopefully, Phase II studies will follow) testing of a recombinant anti-sporozoite vaccine against P. falciparum malaria.

Recent NIAID studies suggest that, in animals, optimum antibody response to the recombinant vaccine may be highly dependent upon the genetic background of the animal. Therefore, it may be important to investigate the influence of the genetic status of recipients (HLA-DR type) upon immune response to the antigen. This may turn out to be an important issue not only for the anti-sporozoite vaccine, but for other future vaccines.

This proposal is to expand the number of subjects given the anti-sporozoite vaccine, both in Phase I and Phase II, in order to study the influence of genetic background upon antibody response, as well as the protective efficacy of the vaccine.

Duration:	2 years
First Year Cost:	$60,000
Total Cost:	$135,000

5. Efficacy Trial for Live, Attenuated Hepatitis A Virus Vaccine

Close to 100,000 cases of Type A viral hepatitis (HAV) are estimated to occur in the United States each year. In underdeveloped countries with poor sanitation, infection with HAV usually occurs early in life, often without jaundice or symptoms, whereas, in developed countries with good sanitation, the infection occurs later in life with more severe manifestations. Unlike hepatitis B virus infections, there is no evidence of sequelae. Prevention rests on vaccination of infants to eliminate the reservoir of inapparent infection. The cost of hepatitis associated with HAV is estimated at $104,569,000 per year in the United States. Recent identification of susceptible animal models and tissue culture systems has resulted in the development of both inactivated (WRAIR and Merck Sharp and Dohme) and live-attenuated vaccines (NIAID and Merck Sharp and Dohme). Limited clinical testing of the corporate products has taken place; testing of the WRAIR vaccine is expected to begin soon; safety and immunogenicity trials (Phase I) of the NIAID vaccine will also begin soon. Upon completion of these trials, there is need for an efficacy trial in a susceptible population.

Discussions with scientists in Greece, India, and the People's Republic of China (PRC) have indicated interest in evaluating the NIAID vaccine. The NIAID hepatitis B vaccine was evaluated in the PRC through an interagency agreement with the CDC under a bilateral (US-PRC) agreement.

Duration:	3 years
First Year Cost:	$150,000
Total Cost:	$450,000

6. Clinical Trial with Different Regimens of Therapy for Systemic Candidiasis

Severe candidal infections, previously rare, have become common problems in medical practices associated with advanced technology for life support. In fact, at the UCLA Medical Center, Candida species are now the fourth most common blood isolate, whereas 20 years ago its isolation was rare. Patients are more susceptible to invasive candidal infections if they have malignancies; have protracted postoperative courses; receive immunosuppressive therapy following organ transplantation; are neonates with low birth weight; have sustained extensive burns; are addicted to heroin; or have AIDS.

Once within the intravascular compartment, the organism may seed virtually any organ and establish foci of infection, commonly multiple microabscesses or small macroabscesses. Unfortunately, because of diagnostic difficulties (blood cultures are an insensitive diagnostic method for diagnosing disseminated disease and there is no readily available serodiagnostic method with an acceptable level of false negatives), the majority of patients with hematogenously disseminated candidiasis are not diagnosed until autopsy.

Most clinicians agree that Amphotericin B (AMB) is the drug of choice for serious forms of candidiasis; however, despite 25 years of clinical use, no firm guidelines for dosage or duration of AMB in systemic candidiasis are available. In addition, newer antifungal agents (miconazole, ketoconazole, itraconazole and others) are on the market or will be available soon for use in candidiasis. To determine how efficacious these newer agents may be, it is imperative that comparative studies be conducted using AMB as a standard.

It is proposed that one clinical form of candidiasis (esophagitis) be studied in neutropenic and non-neutropenic patients. The diagnosis of this form of the disease is most easily attained, clinical end-points are most clear-cut, and there are sufficient numbers of such patients available to achieve the desired sample size. AMB will be compared with ketoconazole or newer antifungal drugs for efficacy and safety. The project will require a multicenter network of 12 or more collaborative investigators.

Duration:	5 years
First Year Cost:	$299,920
Total Cost:	$1,690,672

SBIR

Mr. Early. Doctor, briefly would you tell us how your Institute is using the Small Business Innovative Research program?

Dr. Fauci. The NIAID makes both grant and contract awards under the aegis of the Small Business Innovation Research (SBIR) Program. Proposals are accepted in all scientific areas relevant to the mission of the Institute. The Institute's SBIR grant portfolio amounted to $495,000 in FY 1983, $1,474,000 in FY 1984, and $2,403,000 in FY 1985. In FY 1985 the Institute also awarded 11 contracts for $545,000. The total obligations for SBIR in FY 1986 are estimated at $4,038,000.

A number of SBIR recipients have completed Phase I and have successfully competed for Phase II awards. Results from many of the early awards show great potential.

BUDGET INCREASE

Mr. Early. If an increase over the FY 1987 request is provided, how would you use these additional funds?

Dr. Fauci. Additional funds would be used to fully fund all noncompeting research project grants, and to support additional competing research project grants up to 50 percent of approved grants. This would permit the Institute to capitalize on major technological advances in basic research.

Support for research centers would be increased to fully fund 18 centers, to permit the award of one new Asthma and Allergic Diseases Center devoted to the study of adverse drug reactions, and to add a core outreach demonstration component in each CIRID for the transfer of technology related to basic and clinical immunology.

Additional funding for other research grants would permit the support of 120 research career awards to attract young physicians and scientists into research and to strengthen medical school faculties in the basic and clinical studies on the immune system, biotechnologic advances, and molecular biology.

Minority biomedical support grant funding would be increased as well as high priority conference grants.

Research training would be expanded to permit support of 600 full time training positions in order to provide a continuous influx of new ideas and innovative approaches to removing the barriers to the diagnosis, treatment and prevention of allergic, immunologic and infectious diseases.

Increased funding would be directed to R&D contracts to maintain all ongoing efforts in allergic, immunologic and infectious diseases, to permit the initiation of major new clinical trials cited above; and to permit the award of new contract efforts related to such areas as immune system disorders, transplantation immunology and vaccine and antiviral drug development.

Additional funds for the Intramural Research Program would be used to maintain ongoing efforts and to initiate additional activities in vaccine development and immunotherapy.

Research management and support funding would be increased to better implement and administer the new AIDS Program within the NIAID and to provide for expanded outreach programs in areas such as asthma, childhood immunodeficiences and transplantation.

NEW INITIATIVES DELAYED

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed by lack of funds in the FY 1987 budget?

Dr. Fauci. There are a number of new research initiatives or opportunities that will not be pursued under the FY 1987 request.

Mr. Early. Please provide for the record a list of these, along with a brief description and the funding requirements associated with each.

Dr. Fauci. The following are new initiatives, estimated to cost $40,065,000, to be delayed:

AIDS: The fast pace of research on AIDS has created a number of new opportunities for research since the formulation of the President's Budget. New procedures to identify and quantitate the AIDS virus in a number of body tissues is key to all drug and vaccine development studies. The current virus isolation procedure is extremely expensive and laborious and not highly accurate. In addition, it is not practical for determining the presence of virus in brain tissue. Since it will be necessary to develop drugs which reach the brain, we must have the ability to detect the virus in the brain. Efforts using several approaches can be started to develop better detection methods. Several diverse approaches to the development of vaccines have been proposed. These include using molecular biology to synthesize vaccines and to develop attenuated strains of the HTLV-III virus as well as to develop adjuvants to enhance the immune response to candidate antigens. While there are procedures to evaluate the anti-HTLV-III effect of potential drugs *in vitro*, these can be improved; and practical methods can be developed to screen and evaluate drugs which have potential as immune system enhancers. The development of practical animal models is essential, and projects can be started to screen various African primates and other mammals as well as to develop a candidate mouse model similar to that used with other retroviral diseases. Basic immunologic studies can be expanded such as those to examine the nature of receptor sites for the virus on lymphocytes to determine whether T cell type is correlated with disease susceptibility.

SEXUALLY TRANSMITTED DISEASES: A sexually transmitted disease unit can be established that would concentrate on the area of pelvic inflammatory disease. A herpesvirus disease section in the intramural program would be established to provide an interdisciplinary approach to studies of herpesvirus infections. Recent advances in recombinant DNA and monoclonal antibody technologies can be applied to the development of candidate vaccines against chlamydia, gonorrhea and syphilis. Phase I clinical testing can also be conducted with a currently available synthetic gonococcal vaccine, and large trials of antivirals for treatment of cytomegalovirus disease can be initiated. Basic immunologic studies can be done which can point to the development of a vaccine against the viruses causing genital warts.

HEPATITIS: A live attenuated hepatitis A vaccine is available, and phase II clinical testing of this material can be undertaken.

Using new information on the replication of hepatitis B virus, efforts can be mounted to develop targeted antiviral compounds for treatment of chronic hepatitis B infections. With the advances recently made on the molecular biology of the hepatitis delta agent, studies can be mounted on the pathogenic mechanisms of this virus which may give clues for the development of control measures.

HOSPITAL-ASSOCIATED INFECTIONS: Basic research can be done to develop methods for the prevention and treatment of post-operative infections. In addition, clinical studies of an immune globulin developed against several gram-negative bacteria often responsible for hospital-associated infections can be undertaken.

PARASITIC DISEASES: Basic immunologic research can be done on the parasite causing giardiasis in order to improve diagnosis and treatment. Antigenic studies on strongyloides parasites can be carried out in order to develop a synthetic antigen for performing skin tests.

DIGESTIVE DISEASES: Basic research can be initiated on the roles of methane-producing human intestinal bacteria and pyloric campylobacter in causing a variety of gastrointestinal disorders in order to develop procedures for treatment and prevention.

CYSTIC FIBROSIS/RESPIRATORY DISEASES: A multicenter clinical study of cephalexin for its ability to prevent bacterial colonization in infants with cystic fibrosis can be initiated, as well as efforts to develop a vaccine against Pseudomonas aeruginosa infections in individuals with cystic fibrosis.

There is also a need for efforts on other respiratory diseases such as the development of candidate vaccines against respiratory syncytial and parainfluenza viruses using recombinant DNA technology. A comprehensive study of respiratory diseases, as well as diarrheal diseases, in day care centers can be conducted. Studies on epidemiology and control measures for respiratory diseases would be benefited by the establishment of an Infectious Respiratory Disease Unit within the NIAID extramural program.

PERTUSSIS: Basic research can be expanded on the immunology and pathogenesis of the organism causing pertussis in order to improve diagnostic procedures, and to define the role of mucosal antibody in protection and the roles of individual bacterial components in pathogenesis. This information would help to develop alternate vaccine candidates in the event that the acellular vaccines currently under clinical evaluation are unsuccessful. New recombinant DNA produced antigens can be tested as vaccine candidates, and the potential of antigens known as agglutinogens can be investigated for vaccine potential.

VACCINE DEVELOPMENT: Basic research to develop new generations of vaccines for bacteria such as group B streptococci and pneumococci in which polysaccharide antigens are combined with carrier proteins can be conducted. Research to develop well characterized adjuvants to improve the immune response to existing bacterial polysaccharide vaccines can also be initiated. Research efforts can be mounted, using the new molecular biologic technologies, to develop vaccines against organisms causing diseases such as cholera, Group A streptococci, rabies, dengue and other diseases in which traditional vaccine development efforts have been unsuccessful. A protein engineering unit can be established in the intramural program to explore the development of novel vaccine candidates through genetic engineering techniques. In addition, an intramural vaccine development unit can be established to develop vaccines needed by the public but which are not being developed by industry because they are considered unprofitable.

ASTHMA AND ALLERGIC DISEASES: Basic research on the underlying mechanisms of urticaria and angioedema and on understanding the underlying defect in the asthma triad in order to develop drugs or procedures for treatment can be initiated. Basic studies of the growth of human mast cells in culture would also provide information to better understand and develop treatments for allergic diseases. A clinical study of immunotherapy in the treatment of food allergies can be undertaken along with comparative studies of various available treatments for allergic rhinitis, sinusitis and asthma.

IMMUNOLOGIC DISORDERS: A number of basic research efforts can be initiated to better understand and treat various immunologic disorders. These include: studies on the various mechanisms involved in the development of tolerance in T and B lymphocytes to understand the causes of immunodeficiencies, malignancies and autoimmunity so that therapies can be developed; development of improved methods of immune therapy against infections through the manipulation of genes encoding for receptors; development of procedures to introduce human genes into animals in order to prepare monoclonal antibodies against specific human antigens; studies on genes and cell membrane molecules involved in lymphocyte activation to help in the design of immunoenhancing and immunosuppressive drugs. In addition, a program to acquire and distribute monoclonal antibodies can be developed so that they can be used to selectively attack subsets of human lymphocytes, thereby permitting research to understand the immune system functions and to treat immune system disorders. Referral centers can be set up around the country to concentrate multidisciplinary research efforts for the small number of children who suffer from childhood immunodeficiencies.

TRANSPLANTATION: Studies can be conducted on methods of tolerance induction to aid in development of procedures to minimize the immune response to organ grafts. In addition, monoclonal antibodies against antigens unique to specific organs can be developed which can be used for specific immunosuppression in organ transplant recipients. Mouse models can also be developed in which monoclonal antibodies against histocompatibility antigens can be produced to provide information applicable to use of this approach in humans. A major effort can be initiated on the purification of class I and class II major histocompatibility complex molecules. A better understanding of how these molecules control susceptibillity to disease and how they initiate transplantation rejection would be helpful to improving transplantation procedures.

MAJOR NEW CLINICAL TRIALS: The following clinical trials are ready to begin: 1) efficacy of recombinant DNA hepatitis B vaccines; 2) efficacy of DHPG to prevent cytomegalovirus infection in bone marrow transplant patients; 3) expanded trials of recombinant DNA malaria vaccines; 4) efficacy of live, attenuated hepatitis A virus vaccine; 5) efficacy of monoclonal antibodies in preventing rejection in bone marrow transplantation; and 6) comparison of experimental therapy regimens for systemic candidiasis.

OUTREACH: Outreach efforts can be initiated in the areas of asthma, childhood immunodeficiencies, transplantation and adult immunization. In addition, a core outreach component can be added to each of NIAID's Centers for Interdisciplinary Research on Immunologic Diseases for the transfer of technology related to basic and clinical immunology.

ONGOING INITIATIVES DELAYED

Mr. Early. Doctor, will any significant research initiative currently under way be halted or seriously delayed due to FY 1987 funding levels?

Dr. Fauci. A number of ongoing research activities will be affected by the FY 1987 request level.

Mr. Early. To what extent will there be major reductions in the scope of ongoing or new initiatives because of the FY 1987 funding levels?

Dr. Fauci. Some ongoing activities will be curtailed; others will be terminated.

Mr. Early. For the record, please provide a list of these along with a brief description and the amounts associated with each initiative.

Dr. Fauci. Following are ongoing initiatives, estimated to cost $61,979,000, that will be reduced:

Basic investigator initiated research in allergic, immunologic and infectious diseases supported by research project grants will be reduced as a result of a decrease of 44 competing awards from the FY 1986 revised estimate and the fact that both noncompeting and competing grants to be reduced 13 percent from estimated full funding requirements.

Four competing renewal Asthma and Allergic Diseases Centers will be terminated. In addition, the remaining nine Asthma and Allergic Diseases Centers and five Centers for Interdisciplinary Research on Immunologic Diseases will be reduced an average of 30 percent from estimated noncompeting commitments. Consequently, there will be a decrease in interdisciplinary and clinical research efforts on the causes, prevention and treatment of asthma, immune deficiencies, and autoimmune disorders.

Reductions will also be made in basic and clinical research supported through career awards designed to attract young physicians and scientists specializing in infectious and immunologic diseases into research and academic positions as well as in research training in basic and clinical research in allergic, immunologic and infectious diseases. Support for all basic and clinical intramural research will likewise be reduced; in particular, this will lead to decreased efforts in testing for new recombinant DNA vaccines for hepatitis, the development of new vaccines for Rocky Mountain Spotted Fever, and the development of treatments for allergic diseases.

With respect to applied or targeted activities, research and development, in the following areas will be delayed:

AIDS: Planned supplements to three existing vaccine evaluation units to conduct phase I studies of candidate AIDS vaccines will be postponed as will contract-supported studies on the immunologic defect in AIDS and the development of procedures to correct this defect will be postponed. The amounts for supplements to support studies on the neurologic effects of HTLV-III infection, to be integrated into the ongoing natural history studies, will also be reduced.

Vaccine Development and Testing: Each of four vaccine evaluation units will be reduced; thus, fewer experimental viral and bacterial vaccines will be tested, particularly those in phase I studies. Decreased support for an Influenza Research Unit will reduce the number of clinical trials with newly developed influenza vaccines and laboratory and surveillance studies for evaluating methods of prophylaxis and therapy to be undertaken. A project being conducted by an Infectious Enteric Diseases Study Unit is entirely focused on a trial of rotavirus vaccines; this trial will be terminated before questions of poliovirus interference are answered and before microbiologic diagnostic workups are completed. A laboratory to study the molecular basis of hepatitis pathogenesis and to study the antigen function of respiratory syncytial virus (RSV) polypeptides will be reduced. This will slow down studies on prevention of hepatitis and vaccine development for RSV. Because of the large number of serotypes of the pneumococci, assays of the antibody response to multivalent pneumococcal vaccines are extremely expensive and time-consuming, and there is only one laboratory in the United States equipped to do these assays in support of NIAID and academic investigators developing new experimental vaccines (i.e., protein-polysaccharide conjugates) or studying the effectiveness of existing vaccines in various patient populations (i.e., sickle cell anemia, Hodgkin's disease, traumatic splenectomy). Support for this laboratory will be terminated.

Antiviral Drug Development and Testing: Decreased support for a facility for Infectious Diseases will reduce the number of pathogenesis, prophylaxis, and therapy studies in volunteers for bacterial, parasitic and viral diseases (cholera, shigella, typhoid, *E. coli*, giardia, etc.) to be conducted. Funds for research on the treatment of genital warts with interferon will be reduced. Interferon therapy has been shown effective when administered directly into the lesion; however, for practical administration, it must be given systemically. Studies under way to determine the efficacy of systemic administration will therefore be delayed. In addition, the number and comprehensiveness of antiviral therapeutic studies of herpesviruses will be reduced. Although data exist for immune responses during influenza infections, the impact of antiviral drugs on such responses is largely unknown. Effects of antiviral drugs on immune responses of mice infected with influenza viruses will not be studied due to funding reductions.

Mycotic Disease Therapy: Support related to clinical trials of therapies for systemic mycotic disease will be decreased. A data-coordinating center for collaborative studies of new drug or drug combinations is supported by NIAID. While the patient care costs for these studies are borne by industry, manufacturers would not support comparative studies. This support will be terminated and with it all support of antifungal therapy trials.

Rapid Viral Diagnosis: With reductions in studies on molecular virologic techniques in rapid viral diagnosis, the program to develop rapid diagnosis techniques for viral diseases will be terminated.

AIDS DRUG DELIVERY TO BRAIN

Mr. Early. I have read in the newspapers that some candidate AIDS treatment drugs may or may not be able to move from the blood stream to the brain. How important is it for these drugs to be able to reach the brain?

Dr. Fauci. Data that are currently emerging regarding the isolation of HTLV-III from the central nervous system (CNS), sometimes very early, before many other sequelae of infection are manifest, suggest that the brain may be an important site of virus replication, possibly even some kind of reservoir. It is therefore considered extremely important that antiviral agents get into the CNS. Some drugs do cross the blood-brain barrier reasonably well; others do not. Basic research is being conducted in a number of laboratories to link drugs of interest to chemical carriers that enhance the ability of the complex to cross the blood-brain barrier and actually become concentrated and then slowly released as the carrier is enzymatically removed from the drug in the brain.

SEXUALLY TRANSMITTED DISEASES

Mr. Early. Are you planning any new initiatives in the areas of sexually transmitted diseases other than AIDS?

Dr. Fauci. The Institute intends to maintain and expand its STD research effort to the extent possible. For example, genital herpes research, as part of the overall STD program, will be continued and expanded; the Institute intends to support a new program project grant focused on research to understand the mechanism of latency in genital herpes infections. The Institute is also committed to an expanded research program on chlamydial infections; plans are under way to support a new program project (STD Research Unit) in this area.

Mr. Early. What is the NIAID doing about the problem of pelvic inflammatory disease?

Dr. Fauci. In FY 1985 the Institute supported, as part of its ongoing sexually transmitted disease research program, 18 projects totalling about $3.7 million for research related to pelvic inflammatory disease (PID). In addition, we are going to publish a Request for Applications shortly to initiate a new STD Research Unit that will focus on chlamydial infection, which can cause PID. The chlamydial problem is extraordinarily difficult to control because of the complex life cycle of the chlamydial organism and the fact that it may cause an asymptomatic infection in the female. Once recognized in an individual, however, the infection can be treated with antibiotics. The difficulty lies in bringing suspect patients to a physician before the serious consequences of PID can develop. This problem of inadequate diagnosis or incomplete therapy increases the risk of PID and the spread of the disease.

Mr. Early. How serious is this problem in the United States?

Dr. Fauci. Pelvic inflammatory disease is the most serious consequence of sexually transmitted diseases in women. It is generally the result of an infection with either gonorrhea, chlamydia, or a combination of microorganisms. PID is an infection of the upper genital tract and the female reproductive system and can cause endometritis, tubal infection and scarring, ectopic pregnancy and involuntary sterility. It is estimated that, each year, about 40,000 women become sterile as a result of PID. Further estimates are that approximately 1,000,000 PID cases occur annually, costing about $1.5 billion to the health care system.

HERPES ENCEPHALITIS

Mr. Early. I have heard a lot about the use of acyclovir for treating genital herpes infections. What can you tell us about acyclovir in treating a less well-known disease, herpes encephalitis?

Dr. Fauci. Herpes simplex encephalitis, HSE, remains the most common cause of sporadic fatal encephalitis in the Western World. Currently, HSE is estimated to occur in one in 250,000 to 500,000 individuals per year. In the absence of therapy or following the administration of ineffective antiviral drugs, mortality is in excess of 70 percent and only approximately 2.5 percent of patients overall return to normal function following disease. In the late 1970's, the NIAID Collaborative Antiviral Study Group (CASG) showed convincingly that vidarabine therapy reduced mortality from 70 percent to 44 percent. Recently a comparative trial of vidarabine versus acyclovir was completed by the NIAID CASG and showed that acyclovir therapy further decreased mortality to 19 percent six months after treatment. Thirty-eight percent of patients, irrespective of age, returned to normal function. Although the gain of return to normal from 2.5 percent to 38 percent is quite remarkable, outcome is still not adequate. Improved outcome will be dependent upon earlier and specific diagnosis, drugs of enhanced therapeutic index, and advances in our understanding of CNS immune responses.

BUDGET

Mr. Hoyer. Dr. Fauci, what was your original request to Dr. Wyngaarden for FY 1987? PHS, DHHS, etc.

Dr. Fauci. The NIAID's original request to NIH for FY 1987 was $493,044,000; the NIH estimate to PHS and the PHS estimate to DHHS were consolidated submissions at the NIH level.

Mr. Hoyer. What areas have had to be cut back or not pursued under this budget request which you would have done under your request to Dr. Wyngaarden?

Dr. Fauci. Included in those areas that have been cut back or not pursued are the following:

1) Investigator-initiated basic research in allergic, immunologic and infectious diseases supported by research project grants. Examples are: research to characterize the immune response to proteins of the viruses causing genital warts; research to develop procedures for the prevention and treatment of post-operative and other hospital-associated infections; multidisciplinary research approaches to elucidate the mechanisms of viral pathogenesis; molecular biologic studies on the pathogenic mechanisms of hepatitis delta virus; studies to understand the underlying defect in the asthma triad in order to develop pharmacologic agents to counteract the defect; multidisciplinary projects on mechanisms of mucosal immunity to enteropathogens; and the identification and characterization of, as yet, unrecognized antigens important in asthma and allergies.

2) Four ongoing Asthma and Allergic Diseases Centers (AADCs) as well as two new AADCs to focus on adverse drug reactions, six new Centers for Interdisciplinary Research on Immunologic Diseases (CIRIDs) and expanded outreach activities at existing CIRIDs.

3) Major new clinical trials such as an efficacy trial of hepatitis A and hepatitis B vaccines and trials of antimalarial vaccines, and numerous other contract-supported activities including, among others, the accelerated development of antisera medications to facilitate treatment of asthma, development of monoclonal antibodies against antigens unique to specific transplantable organs, prospective study of neonatal herpesvirus infection, and expansion of clinical facilities to test and evaluate candidate vaccines in humans, as well as vaccine development efforts directed at sexually transmitted diseases and other viral and bacterial diseases.

4) Research career awards and research training in basic and clinical aspects of allergic, immunologic, and infectious diseases.

5) Basic and clinical intramural research including: the establishment of an interdisciplinary, interactive vaccine development unit; expanded studies on pertussis; studies on the genes and cell membrane molecules involved in T and B lymphocyte activation, leading to the design of drugs for use in immunodeficiencies, malignancies, and autoimmune diseases; studies on the underlying mechanisms of allergic and inflammatory diseases; and the establishment of a herpesvirus disease section to provide an

interdisciplinary approach to the study of the pathogenesis and prevention of herpesvirus infections.

6) Expanded outreach and technology transfer activities.

Mr. Hoyer. The justification notes that there will be a decrease of 4 percent from estimated noncompeting commitments. In 1986 the reduction was 7 percent. It further notes a loss of 88 research trainees. Are you concerned over these decreases?

Dr. Fauci. For NIAID, there will be a 13.1 percent decrease from estimated noncompeting commitments for research project grants in FY 1987 compared to a decrease of 8.9 percent in FY 1986. While I am concerned about these decreases as well as the reduction of 88 research trainees, every effort will be made to ensure that the highest priority research and training activities will be supported.

Mr. Hoyer. Were you responsible for allocating these reductions?

Dr. Fauci. I was provided the figures for research project grants (amounting to 70 percent of the NIAID request), but did allocate the amount for training within the remaining funds available to the Institute.

IMMUNIZATION OF CHILDREN

Mr. Hoyer. Dr. Fauci, I am concerned that due to several unrelated occurrences, one of them being the product liability crisis, that we are not paying enough attention to immunization of our nation's children against whooping cough, chickenpox, etc. Doctor, is this a valid concern?

Dr. Fauci. Yes; the United States could face another shortage of diphtheria-tetanus-pertussis (DTP) vaccine should one of the two DTP manufacturers not be able to renew its liability insurance coverage this summer. Lederle Laboratories has threatened to withdraw from the market if it cannot renew such insurance.

Mr. Hoyer. If so, what should we do to address this issue?

Dr. Fauci. The problem of liability for vaccine-associated reactions and injuries has been discussed extensively in the 10 years since the association of Guillian Barre Syndrome with swine influenza vaccine. Between the presentation of the Reports and Recommendations of the National Immunization Work Group, including one on liability, on March 11, 1977, and the publication of the Institute of Medicine Report on Vaccine Supply and Innovation in late 1985, numerous public and private agencies and two major professional associations, the American Academy of Pediatrics and the American Medical Association, have addressed this issue. All have agreed that this is a serious problem to which a solution must be found, although the solutions recommended have varied. Most recently, an Administration task force on tort reform, headed by Assistant Attorney General Richard K. Willard, has made recommendations for dealing with product liability issues. In addition, the Domestic Policy Council Working Group on Vaccine Supply and Liability issued a report in April 1985, dealing with this issue--recommending minor changes in tort law. A subgroup on vaccines and medical devices is expected to issue its report soon and take a consistent approach.

INVOLVEMENT OF NURSES

Mr. O'Brien. What are you doing to involve nurses more in the programs of the institute?

Dr. Fauci. We are involving nurses more in the programs of NIAID in a variety of ways. For example, I recently appointed a nurse as my Special Assistant in my role as NIH AIDS Research Coordinator. NIAID recently funded a fellowship for a nurse investigator to study newborn children with mothers at high risk of AIDS. We work closely on outreach activities with the National Coalition on Immune System Disorders, which has a nurse as the Chairperson of its Steering Committee. We nominated nurses to serve on our National Advisory Council. Members of my staff are currently discussing with lead nursing organizations (National League for Nursing, American Nurses Association) the concept of supporting extramural research grants (Demonstration Projects) in nursing research as they dovetail with the goals of the Institute. Focus on nurses as direct care givers to individuals with AIDS will occur over the next year as an important part of our outreach activities. Nurses are heavily involved in the development and implementation of our intramural biomedical research protocols. The Clinical Nurse Specialist on the Allergy and Infectious Disease Nursing Service at the NIH Clinical Center is co-principal investigator on a Nursing Research Project in AIDS investigating patients' perceptions of care givers. This is a collaborative project between the Allergy and Infectious Disease Nursing Service and a research nurse from the NCI.

HEPATITIS

Mr. O'Brien. The institute is involved in various areas of research on hepatitis and on the development of hepatitis vaccines. What progress has been made in hepatitis research?

Dr. Fauci. Progress in hepatitis research has been made at all levels from basic to developmental research.

Hepatitis B virus (HBV) is estimated to cause 200,000 cases of hepatitis in the United States each year. The outcome of this infection varies from complete recovery to development of the chronic carrier state. A high percentage of these chronic carriers progress to more severe forms of disease such as cirrhosis and primary hepatocellular carcinoma--a form of liver cancer. A vaccine that is effective at preventing this viral infection has been licensed in the United States since 1981. However, it is underutilized due to its expense, the unfounded fear of the presence of other disease agents in it, and the lack of adult interest in vaccination.

Application of the new recombinant DNA (rDNA) technology to HBV led to rapid transfer of this information into vaccine production by several corporations. These new vaccines are expected to have lower production costs than the current plasma-derived vaccine. The NIAID includes HBV vaccines made by rDNA technology in its Accelerated

Development of New Vaccines Program. To promote their development, NIAID sponsors Phase I clinical testing at its vaccine evaluation centers. Pre-clinical developmental work on synthetic peptide and anti-idiotype vaccines is being carried out by several NIAID funded scientists.

NIAID grantees, intramural scientists, and contractors have been instrumental in developing animal models for study of HBV. Pathology, viral replication, immunology, and intervention are all topics of active investigation. For example, the woodchuck was identified by NIAID grantees as a species infected with its own hepatitis virus; contractors have successfully bred animals free of virus in captivity for experimental utilization and have developed assays for the agent and for markers of various disease states. Either acute or chronic disease that progresses to liver cancer can be produced by experimental infection. The greatly shortened time span necessary to develop these sequelae in the woodchuck compared to humans makes it a superb model for basic studies of the acute, chronic, and cancer manifestations associated with hepatitis B infections in man as well as as evaluation of preventive (vaccine) and control (antiviral) measures.

Hepatitis delta virus (HDV) is a recently identified virus that infects only people with pre-existing HBV infection; i.e., it is defective by itself. Severe, often fatal, liver disease may result. NIAID intramural and contract-supported scientists are actively investigating the nature of this new viral agent. They have characterized the virus particle, its genetic information, and protein components, and have developed assays for it.

Hepatitis A virus (HAV) causes about 125,000 cases of hepatitis in the United States annually. This infection is generally asymptomatic in children but may be severe in adults. HAV can be grown in cultured cells; three animal models are available. NIAID, corporate and U.S. Army personnel have independently developed experimental vaccine candidates. Clinical testing of the Army's inactivated vaccine began recently. Both rDNA and synthetic peptide vaccines are in basic research stages.

A large step forward with HAV basic research occurred when NIAID intramural scientists, simultaneously with two corporate groups, utilized rDNA technology to this virus. Monoclonal antibody technology is being used successfully to gain information about the portions of viral proteins capable of eliciting immune responses that neutralize or protect.

In the United States, Non-A, Non-B (NANB) hepatitis is associated with about 125,000 cases of hepatitis each year--many of them transfusion related. Recently, NIAID scientists determined that the agent is a lipid-enveloped virus with RNA as its genetic information. These same scientists, as well as Small Business Innovative Research grantees, are applying modern rDNA and monoclonal antibody technologies to this agent.

A second distinct type of NANB has been identified and is termed "epidemic NANB"; it is found in developing parts of the world. Virus particles have been seen in samples, and several groups are actively working in this area.

INTRAMURAL RESEARCH PROGRESS ON VACCINES

Mr. O'Brien. Last year you noted developments in the intramural research program on new vaccines, particularly for diarrhea, whooping cough, and malaria. Please give us an update on progress on these vaccines.

Dr. Fauci. Rotavirus is a virus that is the single most important cause of diarrhea in infants and young children in developed as well as underdeveloped countries. A rhesus rotavirus vaccine, intended to prevent natural infection by a major strain of rotavirus, is currently undergoing field trials for safety and efficacy. Results from preliminary trials have been encouraging. More definitive information will be forthcoming in May and June of this year. If the vaccine passes these trials, it could be on the market in 3 to 5 years.

As you know, the problem with the current pertussis (whooping cough) vaccine is a relatively high rate of side reactions. One of our Rocky Mountain Laboratories has been successful in cloning and sequencing genes from the pertussis bacterium that produce the toxic products which may be responsible for the side reactions. In the near future, a pertussis vaccine without these products may be available for preliminary tests. We think that this will lead to an effective, safe, and much more acceptable vaccine; however, a lot of work remains to be done.

A recombinant malaria sporozoite vaccine developed by scientists in NIAID in collaboration with WRAIR scientists is very close to Phase I trials--tests for reactivity and safety in human subjects. Depending on the results of these trials, which should be available within 3 to 4 months, Phase II trials--tests for efficacy by challenging vaccinated human subjects--will be initiated. Again, depending on these results, the next phase--field trials--will be undertaken. If all these trials prove the vaccine to be safe and effective, then a vaccine for general use could be available within 2 to 3 years.

CIRIDs

Mr. O'Brien. In light of the continuing pressure on the budget for your institute, what is your prognosis for the future of the Centers for Interdisciplinary Research on Immunologic Diseases (CIRIDs)?

Dr. Fauci. The FY 1987 budget request reflects a reduction in the number of NIAID centers from 18 to 14 and an approximate 30 percent reduction in support for the remaining centers, including the CIRIDs. This reduction will directly affect the CIRIDs' operation, slowing the pace of research activity, knowledge acquisition, and the rapid application of research findings to clinical problems.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

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NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to allergy and infectious diseases, [$383,717,000] *$330,551,000. (Department of Health and Human Services Appropriation Act, 1986.)*

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Amounts Available for Obligation [1]

	1985	1986	1987
Appropriation	$370,965,000	$383,717,000	$330,551,000
Enacted administrative reduction	---	-265,000	---
Sequester order	---	-16,488,000	---
Proposed rescission	---	-1,513,000	---
Subtotal, adjusted appropriation	370,965,000	365,451,000	330,551,000
Comparative Transfer to:			
Office of the Assistant Secretary for Health, for AIDS Projects	-23,273,000	-25,903,000 [2]	---
National Cancer Institute for changes in the Central Services financing mechanisms and formulas	-2,437,000	---	---
Subtotal, adjusted budget authority	345,255,000	339,548,000	330,551,000
Unobligated balance, start of year	---	553,000	---
Unobligated balance, end of year	-553,000	---	---
Unobligated balance lapsing	-365,000	-221,000	---
Total obligations	344,337,000	339,880,000	330,551,000

[1] Excludes the following amounts for reimbursable activities carried out by this account: 1985 -- $2,618,000; 1986 -- $4,679,000; 1987 -- $72,105,000, which includes $67,731,000 for AIDS projects.

[2] The comparative transfer for the appropriation is $27,067,000.

National Institute of Allergy and Infectious Diseases

Budget Mechanism
(Dollars in thousands)

	1986 Appropriation 1/2/		1986 Available after sequestering 1/3/		1986 1/3/ Revised		1987	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research grants:								
Research projects								
Noncompeting.............	1,162	$174,615	1,162	$167,106	1,162	$168,697	1,178	$171,293
Admin. supplemental......	(16)	573	(16)	548	(16)	548	(16)	524
Competing								
Renewal................	235	40,134	235	38,421	201	35,883	188	31,420
New....................	272	33,460	272	32,032	244	31,466	232	26,682
Supplemental...........	1	24	1	24	1	24	1	24
Subtotal, competing..	508	73,618	508	70,477	446	67,373	421	58,126
Subtotal, research projects.........	1,670	248,806	1,670	238,131	1,608	236,618	1,599	229,943
Research centers								
AADC.....................	13	3,546	13	3,380	13	3,380	9	2,139
CIRID....................	5	2,263	5	2,179	5	2,179	5	1,595
Subtotal, research centers.............	18	5,809	18	5,559	18	5,559	14	3,734
Other research								
Research career program..	71	3,979	68	3,809	68	3,809	68	3,979
Minority biomedical support................	(9)	460	(9)	440	(9)	440	(9)	460
Other....................	11	877	11	839	11	839	11	914
Subtotal, other res....	82	5,316	79	5,088	79	5,088	79	5,353
Total, research grants.....	1,770	259,931	1,767	248,778	1,705	247,265	1,692	239,030

Training								
Individual awards								
Noncompeting.............	51	1,272	51	1,272	51	1,272	38	989
Competing, new...........	34	884	18	450	18	450	17	425
Subtotal, individ...	85	2,156	69	1,722	69	1,722	55	1,414
Institutional awards								
Noncompeting.............	358	8,155	358	8,161	358	8,161	277	6,510
Competing								
Renewal................	29	550	22	528	22	528	26	621
New....................	19	392	14	359	14	359	17	438
Subtotal, inst.......	406	9,097	394	9,048	394	9,048	320	7,569
Total, training............	491	11,253	463	10,770	463	10,770	375	8,983
Research and development contracts.................	60	18,134	57	17,354	57	17,354	47	15,235
					FTEs		FTEs	
Intramural research..........		51,566		49,133	519	49,133	519	51,492
Research management and support....................		16,054		15,358	186	15,358	186	15,811
TOTAL......................		356,938		341,393	705	339,880	705	330,551

1/ Reflects an enacted administrative reduction of $265,000 and a carryover in obligated funds of $553,000.

2/ Reflects a comparable transfer of $27,067,000 to the Office of the Assistant Secretary for Health for AIDS projects.

3/ Reflects a consultant services (Section 515 of the Treasury-Postal Service Appropriation Act, 1985) withholding of $221,000 and a comparable transfer of $25,903,000 to the Office of the Assistant Secretary for Health for AIDS projects.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

CROSSWALK - 1986 Appropriation

(Dollars in thousands)

	MECHANISM								
	Research Grants			Training Programs					
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management and Support	Total
Immunology, allergic and immunologic diseases............	$101,098	$5,809	$2,036	$937	$4,031	$3,376	---	---	$117,287
Microbiology and infectious diseases.	147,708	---	3,280	1,219	5,066	14,758	---	---	172,031
Intramural research...	---	---	---	---	---	---	$51,566	---	51,566
Research management and support.........	---	---	---	---	---	---	---	$16,054	16,054
Total.......	248,806	5,809	5,316	2,156	9,097	18,134	51,566	16,054	356,938

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

CROSSWALK - 1986 Available After Sequestering

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM								
	Research Grants			Training Programs					
	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management and Support	Total
Immunology, allergic and immunologic diseases............	$96,761	$5,559	$1,949	$749	$4,013	$3,345	---	---	$112,376
Microbiology and infectious diseases.	141,370	---	3,139	973	5,035	14,009	---	---	164,526
Intramural research...	---	---	---	---	---	---	$49,133	---	49,133
Research management and support.........	---	---	---	---	---	---	---	$15,358	15,358
Total.......	238,131	5,559	5,088	1,722	9,048	17,354	49,133	15,358	341,393

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

CROSSWALK - 1986 Revised Estimate

(Dollars in thousands)

	MECHANISM								
	Research Grants			Training Programs					
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management and Support	Total
Immunology, allergic and immunologic diseases............	$96,146	$5,559	$1,949	$749	$4,013	$3,345	---	---	$111,761
Microbiology and infectious diseases.	140,472	---	3,139	973	5,035	14,009	---	---	163,628
Intramural research...	---	---	---	---	---	---	$49,133	---	49,133
Research management and support.........	---	---	---	---	---	---	---	$15,358	15,358
Total.......	236,618	5,559	5,088	1,722	9,048	17,354	49,133	15,358	339,880

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

CROSSWALK - 1987 Congressional Justification

(Dollars in thousands)

	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management and Support	Total
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional				
Immunology, allergic and immunologic diseases............	$93,434	$3,734	$2,025	$615	$3,413	$3,252	---	---	$106,473
Microbiology and infectious diseases.	136,509	---	3,328	799	4,156	11,983	---	---	156,775
Intramural research...	---	---	---	---	---	---	$51,492	---	51,492
Research management and support.........	---	---	---	---	---	---	---	$15,811	15,811
Total.......	229,943	3,734	5,353	1,414	7,569	15,235	51,492	15,811	330,551

National Institute of Allergy and Infectious Diseases

Summary of Changes

1986 Current estimated obligations	$339,880,000
1987 Estimated obligations	330,551,000
Net change	-9,329,000

	1986 Base	Change from Base
Increases:		
A. Built-in:		
1. Within grade increase	$27,258,000	+$422,000
2. Federal Employees Compensation Fund increase	121,000	+24,000
3. FTS rate increase	612,000	+100,000
4. Payment for centrally furnished services	18,111,000	+1,868,000
5. Increased cost of laboratory supplies, materials and other expenses	19,122,000	+1,296,000
Subtotal		+3,710,000
B. Program:		
1. Research projects:		
a. Noncompeting continuations converting from competing status	169,245,000	+60,643,000
b. Competing (new, renewals and supplementals)	67,373,000	+58,126,000
2. Research centers:		
a. Noncompeting continuations converting from competing status	2,678,000	+2,359,000
3. Other research:		
a. Noncompeting continuations converting from competing status	5,042,000	+193,000
b. Competing (new and renewals)	46,000	+415,000
4. Individual training awards:		
a. Noncompeting continuations converting from competing status	1,272,000	+490,000
b. Competing (new and renewals)	450,000	+425,000

Summary of Changes -- continued

	1986 Base	Change from Base
5. Institutional training awards:		
a. Noncompeting continuations converting from competing status..................	$8,161,000	+$1,016,000
b. Competing (new and renewals)...............	887,000	+1,059,000
Subtotal............		+124,726,000
Total, increases..		+128,436,000
Decreases:		
A. Program:		
1. Research projects:		
a. Noncompeting completed or converting to competing status..................	169,245,000	-58,071,000
b. Competing completed or converting to non-competing status.........	67,373,000	-67,373,000
2. Research centers:		
a. Noncompeting completed or converting to competing status..................	2,678,000	-999,000
b. Competing completed or converting to noncompeting status..................	2,881,000	-2,881,000
c. Competing (new and renewals)...............	2,881,000	-304,000
3. Other research:		
a. Noncompeting completed or converting to competing status..................	5,042,000	-297,000
b. Competing completed or converting to noncompeting status..................	46,000	-46,000
4. Individual training awards:		
a. Noncompeting completed or converting to competing status..................	1,272,000	-773,000
b. Competing completed or converting to noncompeting status..................	450,000	-450,000

Summary of Changes -- continued

	1986 Base	Change from Base
5. Institutional training awards:		
a. Noncompeting completed or converting to competing status..................	$8,161,000	-$2,667,000
b. Competing completed or converting to noncompeting status..................	887,000	-887,000
6. Research and development contracts:		
a. Continuation...	17,354,000	-2,119,000
7. Intramural research: Program decrease in lower priority areas.......................	49,133,000	-592,000
8. Research management and support: Program decrease in lower priority areas.....	15,358,000	-306,000
Subtotal.................		-137,765,000
Total, decreases.......		-137,765,000
Total, net change..................		-9,329,000

National Institute of Allergy and Infectious Diseases

Budget Authority by Activity
(Dollars in thousands)

	1986 1/ Appropriation Amount	1986 Available after 2/ Sequestering Amount	1986 Revised FTEs	1986 Revised 2/ Amount	1987 FTEs	1987 Amount
Immunology, allergic and immunologic diseases..........	$117,287	$112,376	---	$111,761	---	$106,473
Microbiology and infectious diseases..........	172,031	164,526	---	163,628	---	156,775
Intramural research..........	51,566	49,133	519	49,133	519	51,492
Research management and support.......	16,054	15,358	186	15,358	186	15,811
Total Obligations.....	356,938	341,393	705	339,880	705	330,551
Unobligated balance, start of year.....	-553	-553		-553		---
Unobligated balance, lapsing...........	---	221	---	221	---	---
Total budget authority.......	356,385	341,061	705	339,548	705	330,551

NOTE: All 1986 columns reflect an enacted administrative reduction of $265,000.

1/ Reflects a comparable transfer of $27,067,000 to the Office of the Assistant Secretary for Health for AIDS projects.

2/ Reflects a comparable transfer of $25,903,000 to the Office of the Assistant Secretary for Health for AIDS projects.

National Institute of Allergy and Infectious Diseases

Obligations by Object

	1985 Actual	1986 Estimate	1987 Estimate
Total number of full-time perm pos....	652	652	652
Total compensable workyears:			
Full-time equivalent employment.....	766	725	725
Full-time equivalent of overtime and holiday hours.................	9	9	9
Average ES salary......................	$66,232	$62,920	$62,920
Average GS grade.......................	9.14	9.14	9.14
Average GS salary......................	28,224	26,813	26,813
Average salary, grades established by act of July 1, 1944 (42 USC 207)........................	35,361	33,593	33,593
Average salary of ungraded positions..	23,206	22,046	22,046
Personnel compensation:			
Permanent positions.................	$15,624,000	$16,059,000	$16,316,000
Positions other than permanent......	5,853,000	5,768,000	5,858,000
Other personnel compensation........	966,000	962,000	977,000
Special personnel services..........	900,000	885,000	885,000
Subtotal, personnel compensation..	23,343,000	23,674,000	24,036,000
Personnel benefits.....................	3,536,000	3,584,000	3,648,000
Benefits for former personnel.........	46,000	60,000	60,000
Travel and transportation of persons..	791,000	914,000	963,000
Transportation of things...............	220,000	256,000	247,000
Rent, communications and utilities....	1,697,000	1,767,000	1,903,000
Printing and reproduction..............	438,000	488,000	508,000

Other services:			
Project contracts	18,672,000	17,354,000	15,235,000
Centrally furnished services	17,104,000	17,686,000	19,483,000
Standard level user charge	691,000	425,000	496,000
Other	8,923,000	7,621,000	7,727,000
Supplies and materials	6,880,000	6,294,000	6,459,000
Equipment	1,879,000	1,722,000	1,773,000
Interest and dividends	1,000	--	--
Grants, subsidies & contributions	260,116,000	258,035,000	248,013,000
Total	344,337,000	339,880,000	330,551,000

National Institute of Allergy and Infectious Diseases

Significant Items in Senate Appropriations Committee Report

Item	Action Taken or To Be Taken
1986 Senate Report	
Malaria Vaccine Development	
1. "Utilizing the powerful new techniques of recombinant DNA technology and monoclonal antibodies, NIAID staff and their collaborators in several institutions have developed a candidate vaccine.... The Committee recognizes the importance of this recent accomplishment and directs the institute to continue to give this research a high priority." (page 82)	1. Two vaccines, both acting against the sporozoite stage of Plasmodium falciparum, the most deadly of the human malarias, have been produced as a result of extramural and intramural research support. Human trials of these vaccines will begin in early 1986. Investigators are being supported to develop a sporozoite vaccine for other species of Plasmodium as well as vaccines for possible combination with the sporozoite vaccine to provide protection at different stages of the parasite's life cycle. A number of antigens have been isolated and characterized and are being tested for protective effects. A major effort is being supported in this area of research that is complicated by the large number of antigens to be studied and antigenic variation within the parasite species.

International Health Research/Tropical Diseases

2. "The Committee is aware that NIAID is one of the few organizations in the world with a primary commitment to support free-ranging research in immunology and microbiology related to tropical diseases including very basic research on parasites and host responses to them. In addition, the Institute's commitment to international research is very strong, and evidence of its contribution is the significant progress in the development of a malaria vaccine. The Committee concurs with these activities and highly recommends that the current momentum be maintained. In addition, the Institute should continue its commitment to the training of researchers in tropical disease research as well as in the dissemination of research advances to the developing world." (page 82-83)	2. It is estimated that 500 to 1,000 million people, primarily in developing countries, suffer from tropical diseases and parasitic infections. Many more are at risk, including Americans visiting or working in these areas. The NIAID supports research and research training on a number of these important diseases in the United States and at overseas sites in collaboration with foreign investigators. Together these investigators are working at the bench and in the field to develop accurate and rapid diagnostic techniques. The Institute remains committed to the training of researchers and the dissemination of research results in tropical diseases and will continue to encourage quality research applications in this area.

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1986 Amt. Authorized	1986 Estimate	1987 Amt. Authorized	1987 Budget Request
Research and Investigation.......	Section 301	42§241	Indefinite	$329,110,000	Indefinite	$321,568,000
National Institute of Allergy and Infectious Diseases............	Section 446	42§285f	Indefinite		Indefinite	
National Research Service Awards.	Section 487	42§288 -1	$244,000,000 1/	10,770,000	$260,000,000 1/	8,983,000
Total Budget Authority.........				339,880,000		330,551,000

1/ This training authority is shared with other research training programs of the National Institutes of Health; the Alcohol, Drug Abuse, and Mental Health Administration; and the Health Resources and Services Administration.

National Institute of Allergy and Infectious Diseases

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation[1]
1978	154,901,000	158,341,000	163,299,000	162,341,000
1979	166,802,000	183,198,000	183,198,000	191,328,000
1980	190,483,000	215,402,000	200,000,000	215,364,000
1981	230,375,000	232,355,000	232,779,000	232,077,000
1982	214,504,000[2]	259,763,000	246,452,000	235,895,000
1983	246,043,000	276,367,000	270,795,000	279,122,000
1984	289,428,000	307,128,000[3]	304,228,000[3]	317,663,000
1985	325,379,000	355,728,000[4]	375,091,000	368,528,000
1985 Proposed Rescission	-428,000			
1986	383,452,000	371,941,000[5]	429,453,000	383,452,000
1986 Sequester	-16,488,000			
1986 Proposed Rescission	-1,513,000			
1987	330,551,000			

[1] Reflects enacted supplementals, rescissions, and reappropriations.

[2] Reflects the September amendment; the original request was $243,755,000.

[3] Excludes $8,619,000 in NRSA training programs not considered.

[4] Excludes $8,690,000 in NRSA training programs not considered.

[5] Excludes $11,382,000 in NRSA training programs not considered.

National Institute of Allergy and Infectious Diseases

Justification

	1986 Appropriation	1986 Available after Sequestering	1986 Revised		1987	
	Amount	Amount	FTEs	Amount	FTEs	Amount
Immunology, allergic and immunologic diseases........	$117,287,000	$112,376,000	---	$111,761,000	---	$106,473,000
Microbiology and infectious diseases........	172,031,000	164,526,000	---	163,628,000	---	156,775,000
Intramural research........	51,566,000	49,133,000	519	49,133,000	519	51,492,000
Research management and support.........	16,054,000	15,358,000	186	15,358,000	186	15,811,000
Total.......	356,938,000	341,393,000	705	339,880,000	705	330,551,000

General Statement

The National Institute of Allergy and Infectious Diseases (NIAID) has the mission of improving this Nation's ability to prevent and control infectious diseases and diseases resulting from disorders of the immune system. To accomplish this goal, the NIAID conducts basic and clinical research in its laboratories in Bethesda, Maryland, and Hamilton, Montana, and supports through extramural mechanisms, research and research training in institutions throughout the United States. To achieve the ultimate goal of diagnosing, treating and preventing infectious and immunologic diseases, the Institute supports research projects in a large number of related research disciplines. These projects include basic research efforts in the disciplines of virology, parasitology, bacteriology, mycology, molecular biology, immunobiology, immunochemistry, immunoregulation, immunogenetics, transplantation biology and immunopathology. Applied and clinical investigations, including clinical trials of preventive and treatment agents and procedures, are supported in the areas of infectious diseases and allergy and clinical immunology.

A major objective of the NIAID's research program is a thorough understanding of the immune system, a discrete organ system of the body whose proper functioning is essential to good health. Damage to the immune system from outside agents or from malfunctions within the body can have profound effects on the functions of all other body organs. The development of agents and procedures to defend against attacks on the immune system and to overcome malfunctions and restore damaged immune function are important goals.

The prevention and treatment of infectious diseases caused by viral, bacterial, fungal and parasitic agents is also a major objective of the NIAID research program. This includes infectious diseases endemic and epidemic in the United States as well as those typically included in the designation, "tropical diseases," which are responsible for much illness and death in developing countries.

While certain disease areas of primary interest to the NIAID may also be of interest to other Institutes within NIH, the NIAID is virtually the only source of Federal research support for investigators conducting research in allergic diseases, the common respiratory and gastrointestinal infections, sexually transmitted diseases, bacterial pneumonias and meningitis, fungal infections and tropical medicine.

Allergic and infectious diseases continue to represent a serious health problem to American citizens. It is established that they account for about one-third of all visits to physicians, with medical costs in excess of $2 billion per year. In addition, approximately $2.5 billion is spent annually on drugs for treatment of these conditions. While many infections and immunologic disorders are life-threatening and gain higher visibility, it is important to recognize that infections such as the common cold and influenza and allergic conditions such as asthma are responsible for much work loss and school absenteeism. They, therefore, extract an enormous economic and social toll in this country.

The expertise of NIAID extramural and intramural staff, coupled with the momentum of ongoing research in basic areas of virology, molecular biology and immunology and in clinical infectious diseases and immunoregulation, allowed the Institute to respond quickly to the public health emergency presented by the acquired immunodeficiency syndrome (AIDS). It is now known that this syndrome is an infectious disease of the immune system that predisposes its victims to other opportunistic infections and tumors. It is also a sexually transmitted disease with important implications for the field of tropical medicine. All these areas are of primary concern to the mission of the NIAID, and this Institute has accepted a major responsibility for research on this devastating disease.

Since the recognition of AIDS in 1981, the NIAID's Intramural Research Program has steadily increased its basic and clinical research on this disease and has been responsible for the precise delineation of the immune defect that is characteristic of the disease. In recognition of the need for increased extramural effort, the NIAID established an Acquired Immunodeficiency Syndrome Program at the organizational level of the previously existing Microbiology and Infectious Diseases Program and the Immunology, Allergic and Immunologic Diseases Program. This AIDS Program will administer grants and contracts for 1) studies of the epidemiology and natural history of the disease, including international epidemiology studies; 2) the development and clinical testing of antiviral agents active against HTLV-III, the virus that causes AIDS, of agents and procedures for reconstitution of the immune system and of agents for treatment of the opportunistic infections that kill individuals with AIDS; and

3) the development and clinical testing of candidate vaccines for prevention of HTLV-III infection.

While the NIAID has responded to the AIDS crisis by mounting a major effort on this disease, it is important to recognize that the Institute was able to respond to this need because of the expertise and information gained through research in the other infectious disease and immunology areas within the responsibility of the Institute.

Overall Budget Policy

The 1987 budget request for NIAID is $330,551,000, a decrease of $9,329,000 from the comparable 1986 level of $339,880,000. Excluded from the request are $67,731,000 for AIDS which are budgeted in the single AIDS appropriation in OASH. Comparable AIDS expenditures are $25,903,000 in 1986 and $23,273,000 in 1985. The Institute will direct 87 percent of its extramural funds in support of investigator-initiated research project grants. About 3 percent of extramural funds will be invested in research training, while research centers and research and development contracts will account for about 7 percent of extramural funding in the budget request.

In 1986, 446 new and competing research project grants will be supported. Both competing and noncompeting grants will be funded at levels that reflect about a 1 percent and 9 percent reduction, respectively, from estimated study section recommended amounts. In 1987, the request will support 421 competing research project grants, a reduction of 25 from 1986, at an average cost of $138,067. This represents an 8.6 percent decrease in average cost from 1986 and a 10.4 percent reduction from full recommended levels. Historically, these reductions have averaged 3 to 4 percent for NIH. The budget request also provides support for 1,178 noncompeting research project grants at an average cost of $145,410. This represents a 0.1 percent increase in average cost over 1986 and a 10.5 percent reduction from full commitment levels. Historically, these reductions have averaged 1 percent. These levels will be achieved by limiting indirect costs and negotiating direct costs downward.

The 1987 request includes funding for 14 research centers, a decrease of 4 from 1986. No competing centers will be awarded. In addition, the centers will be reduced an average of 30 percent from estimated noncompeting commitments. In 1985 centers were awarded at full cost, and in 1986 the reduction was 7 percent.

Funds for other research will permit 2 competing to be made for a total of 68 research career program awards, the same as 1986. Modest increases are provided for MBS and other research grants that reflect the current services level for these two mechanisms.

The number of research trainees to be supported will be decreased by 88 from 1986 to a total of 375, and the funding level is decreased by $1,787,000 to $8,983,000. The 1982 policies on the payment of indirect costs and institutional allowances will be continued in 1987.

Funding for R&D contracts will be reduced by $2,119,000 from 1986 to a total of $15,235,000. The number of contracts supported will decrease by 10. In accordance with Section 515 of the Treasury and Postal Services Appropriation Act of 1985, a total of $421,000 has been withheld from support for intramural research and research management and support in 1986. Funding for these two mechanisms in FY 1987 are $51,492,000 and $15,811,000, respectively. The 1987 levels reflect increases for administrative mandatories offset by selected program decreases.

Program Accomplishments

NIAID intramural scientists and investigators supported through extramural grants and contracts have made significant advances in basic and clinical research in infectious diseases and in allergic and immunologic diseases.

Considerable progress has been made by the NIAID in AIDS research. Studies of the epidemiologic, immunologic and virologic aspects of AIDS in tropical countries such as Zaire, Kenya, Haiti and Trinidad have suggested a high incidence of HTLV-III infection, particularly in prostitutes. These studies also suggest transmission via re-use of unsterilized needles, blood transfusion and transplacental passage of virus. Household studies in Zaire have failed to demonstrate casual contact transmission and have reinforced evidence of sexual transmission and mother-to-infant transmission.

During the past year the viral agent that causes AIDS (HTLV-III, a retrovirus) has been studied extensively within NIAID and NCI laboratories and in extramurally supported institutions. The virus isolated from several geographical locations has been characterized by molecular biologic techniques and the DNA cloned. Comparison of the DNA from isolates obtained from different geographic areas have revealed heterogeneity in the genome, largely within the region of the viral envelope genes. Isolates from Central Africa were significantly different from a variety of North American isolates. Differences were seen also in biologic properties, especially in growth rates and ability to infect target tissues. These observations have significant implications for vaccine development.

Studies of the molecular structure of the virus have led to the development of an infectious clone, which currently is being propagated in a rhabdomyosarcoma cell line. In addition, DNA probes have been made that have been used to detect virus in peripheral blood and bone marrow. A variety of DNA clones coding for different regions of the AIDS virus genome have been expressed in prokaryotic systems (i.e., bacterial cells such as Escherichia coli). The expressed proteins should provide excellent reagents for delineation of the precise nature of serologic and cellular immune responses to the virus. A variety of monoclonal antibodies against individual viral components have also been developed. These monoclonal antibodies may be of clinical relevance in that they may block the activity of the virus.

Animal models of AIDS are being developed. NIAID scientists were the first to transmit the infection to a nonhuman primate by inoculating chimpanzees with plasma from patients with lymphadenopathy syndrome. In a strain of mice infected with a murine leukemia retrovirus, a model for the lymphadenopathy syndrome seen in AIDS Related Complex (ARC) has been developed. Further study of these models should assist the development of preventive and therapeutic approaches to AIDS.

Intramural researchers in collaboration with NCI investigators have demonstrated in phase I studies the safety and efficacy of Suramin in suppressing retroviral replication in patients with AIDS. Clinical efficacy has not yet been proven and will await further large-scale phase II studies.

A defect in the ability of lymphocytes from AIDS patients to kill infected target cells in vitro has been corrected by a lymphocyte product, interleukin-2

(IL-2). As a result, clinical studies to try to reconstitute the impaired host defenses in AIDS with IL-2 have been initiated. Gross and microscopic regression of one of the cancers observed in AIDS patients, Kaposi's sarcoma, has been seen following treatment with IL-2. In other studies, attempts at cellular reconstitution have been made by bone marrow transplantation and lymphocyte transfusion in identical twins. Partial transient correction of the impaired immune system was achieved by these techniques. Thus, it is possible to improve transiently the immune dysfunction in AIDS; but the data indicate that for this immune reconstitution to be of clinical relevance, it will have to be done in connection with successful therapy against the etiologic agent.

Cytomegalovirus (CMV) infection is a particularly severe problem in patients with AIDS and over the past year NIAID scientists have treated AIDS patients infected with cytomegalovirus with dihydroxymethylpropoxymethylguanine (DHPG). CMV remissions have been achieved although a major problem remains in that the remissions are short-lived and chronic maintenance therapy is required. NIAID-supported contractors have synthesized and tested several compounds targeted for action against CMV. Several appear to interfere with the replication of CMV in host cells and are ready for testing in animal models.

A major emphasis by intramural scientists has been on the development of new vaccines for use against AIDS as well as numerous other illnesses. An important advance has resulted from the demonstration that multiple viral genes can be inserted in the vaccinia virus, which was used to eradicate smallpox. An envelope gene of HTLV-III has been expressed in a vaccinia virus vector, and sera from AIDS patients react with the recombinant protein. In addition, mice immunized with the recombinant virus produced antibodies that reacted with the envelope protein of HTLV-III. Efforts to determine the possible prophylactic value of recombinant vaccinia virus in preventing HTLV-III infection in animals are in progress.

Important research advances have been made in the regulation of immune responses. A high molecular weight B cell growth factor has been identified and purified, which enhances the proliferation of human B lymphocytes, cells that produce antibodies. This factor may be responsible for the pathogenesis of certain autoimmune diseases characterized by hyperactive B cells. A monoclonal antibody directed against this factor has been developed, and cloning of the gene coding for the factor is in progress. Studies on the use of drugs to modulate B cell function are showing some promise.

Intramural investigators have made substantial contributions in elucidating the nature of the T cell receptor for antigen, including cloning the genes for this previously elusive molecule.

Survival rates for all types of solid organ transplants have improved markedly. Currently 75 percent of heart transplants, 70 percent of liver transplants and 75-80 percent of kidney transplants survive for three years. These favorable statistics have resulted from research in three areas: 1) immunosuppression of the rejection response; 2) enhancement of organ preservation techniques; and 3) improvements in donor-recipient matching.

Molecular biology methods are being utilized for improved donor-recipient matching. The exact structure of the human major transplantation antigen (the tissue-specific histocompatibility complex) is being elucidated by a study of gene structure and preparation of monoclonal antibodies to proteins prepared from cloned genes. The reagents developed through these techniques are being used to identify those cell surface molecules, present on donor organs, which must be matched in donors and recipients in order to prevent rejection.

NIAID has recently begun a five-year multicenter study of the efficacy of injection treatments in adult asthmatics allergic to either ragweed or house dust mites. Also under way is investigation on the efficacy of injection treatment programs for those at risk of allergic reactions to animal pets or through occupational exposures.

Severe allergic reactions to fire ant stings are seen increasingly as a result of the migration of this insect beyond the southern and southwestern sections of the United States. Studies are under way to identify active venom components and to develop materials for injection treatments of this condition.

Several lines of investigation are providing valuable leads for increased understanding of the multiplicity of causes and triggering mechanisms in the production of asthma. While the association of infections with exacerbation of asthmatic episodes has long been recognized, new studies are providing valuable leads for defining a specific role for virus infection in asthma. Laboratory data suggest that influenza virus may cause increased release of histamine from basophil cells and an alteration in other white blood cell (granular leukocyte) functions. Studies on parainfluenza are pointing to the tissue level at which this virus affects cell receptors responsible for bronchial muscle contractile responses to inflammatory substances resulting in hyperreactivity of the airways.

A major advance in the assessment of asthma has been the development of fiber-optic bronchoscopy and bronchoalveolar lavage techniques to examine cell populations before and after provocation testing. Preliminary data point to the importance of immunological responses in mediating asthma and can be expected to provide important information to the pharmaceutical chemist for the design of specific anti-asthmatic drugs.

The syndrome of exercise-induced anaphylaxis, described recently, is characterized by the onset of itching, warmth, generalized hives, gastrointestinal symptoms, collapse and upper respiratory distress. Research based upon biochemical and electron microscopic study of tissue sections provide evidence that exercise-induced anaphylaxis is a distinct form of physical allergy associated with activation of mast cell degranulation and resultant secretion of chemical mediators of inflammation.

A number of diseases are due to a functional disorder of the immune system which causes antibodies to be produced to attack one's own tissues organs. Examples of these diseases are systemic lupus erythematosus, rheumatoid arthritis, juvenile diabetes mellitus, myasthenia gravis and multiple sclerosis. Specific "therapeutic" antibodies directed toward the autoantibodies have shown success in models of myasthenia and multiple sclerosis, and preliminary clinical trials are under way in the latter case.

In an NIAID-supported clinical trial, intravenous gamma globulin appeared to prevent the development of myocarditis in children with Kawasaki's disease.

It has also proved of value in temporarily aiding immune-suppressed children and some immunodeficient adults in recovering from common infections.

NIAID has provided the leadership to develop an aspergillosis case registry, which provides materials and expertise for diagnosing and treating allergic bronchopulmonary aspergillosis, a condition seen in the lungs of individuals compromised through diseases such as cystic fibrosis and through various occupational hazards.

NIAID-supported extramural investigators have recently characterized two new proteins that show potential for future development of a vaccine against gonorrhea. One is an outer membrane protein antigen, termed H-8 antigen, that appears to be common to all pathogenic strains of Neisseria, the genus to which the gonorrhea organism belongs. The other is a newly discovered iron-regulated protein that elicits an antibody found in all patients with naturally acquired infections.

Cystic fibrosis (CF) is the most common genetic disease in the Caucasian race. In the United States, approximately 15,000 cases are reported annually. Victims have a difficult and shortened life span because of chronic lung and airway damage. The primary causal agent of this pulmonary syndrome is the bacterium Pseudomonas aeruginosa. Research is under way to evaluate methods to protect against Pseudomonas lung infection. A candidate material for a vaccine may be the mucoid exopolysaccharide (MEP) antigen found in a majority of Pseudomonas strains infecting CF patients. It was demonstrated in a guinea pig model that this capsular complex sugar was protective against lung infection, by both active and passive immunization.

Exposure to the principal etiologic agent of genital herpes (Herpes Simplex Virus-type 2, HSV-type 2) can now be ascertained serologically. A newly defined protein (gG) of herpes simplex virus serologically differentiates HSV-type 1 from HSV-type 2. The discovery of this highly specific protein adds a new dimension to serodiagnosis of herpes and to epidemiological studies on the prevalence of the disease. One such study in adults showed that only 25 percent of individuals with serologic evidence of past HSV-type 2 infections had any history of clinical disease. These studies also confirmed that either HSV-type 1 or HSV-type 2 could cause genital herpes, but, of those with clinical histories, 80 percent had evidence of HSV-type 2 infections.

NIAID-supported investigators have succeeded in characterizing and mapping the genes of respiratory syncytial virus (RSV), an important cause of respiratory infections in children. The RS virus has four surface proteins. Two of these proteins, the G protein and the F protein, are thought to be important because they contain the antigenic determinants of the virus and, like the influenza hemagglutinin, perform important functions in replication of this virus. Studies are in progress to develop vaccines from these proteins.

The search for effective antivirals for RSV infections has also received new impetus. A family of compounds (amidines), which inhibit specific cleavage reactions in the maturation of RSV, is under study. Encouraging results also have been obtained with an antiviral drug (ribavirin) administered via aerosol. It has been shown to be effective in the treatment of severe RSV infections of children.

About 200,000 cases of hepatitis B virus (HBV) infection are estimated to occur yearly in the United States. In addition, there are at least 800,000 chronic carriers in the United States and 200 million worldwide. A high percentage of chronic carrier disease leads to cirrhosis of the liver, which can then progress to primary hepatocellular carcinoma (PHC), a form of liver cancer. There are 250,000 cases of PHC worldwide each year. The currently licensed HBV vaccine is highly effective in adults and, in combination with hepatitis B immune globulin, is effective in preventing perinatal transmission. The current plasma-derived vaccine is not widely used, however, because of unsubstantiated fears that it might be contaminated with the AIDS virus and because of its high cost. Using recombinant DNA and other new technologies, investigators are developing second-generation less expensive hepatitis B vaccines. The plasma-derived vaccine consists of a surface antigen from the hepatitis B virus (HBV). In the process of cloning, sequencing and studying the expression of HBV, NIAID grantees have identified another protein, designated PreS; there is evidence that its presence with the S antigen in a vaccine will provide better protection than S alone. In their approach to a genetically engineered vaccine, several corporations are producing vaccines containing both proteins.

In 1978, the woodchuck was shown by NIAID grantees to be infected with its own hepatitis virus (WHV, similar to HBV). Woodchucks also developed the complications of hepatitis seen in humans--chronic infection and primary hepatocellular carcinoma. Under an NIAID-NCI collaborative effort, scientists at Cornell University have successfully bred woodchucks in captivity that are free of WHV. These laboratory-derived animals were experimentally infected with WHV to cause hepatitis. Conditions were established that led to either acute infection or the chronic carrier state. Within a time span between 1½ and 3 years, the animals with chronic disease developed liver cancer. This finding affirms the human epidemiological data that demonstrated a correlation between the HBV chronic carrier state and liver cancer. Moreover, it establishes an animal model for this severe human disease. Preliminary experiments indicate that infection can be prevented by immunization with vaccine prepared by the same techniques used for human vaccines.

Hepatitis delta virus (HDV) is a recently identified defective virus that may infect people who have acute or chronic HBV infections. Severe liver disease may result, often leading to death. Using recombinant DNA technology, scientists have now cloned the complete genome of HDV and sequenced it. This information along with other characteristics recently discovered should provide a more detailed understanding of the virus and the disease it causes, as well as enhance the development of prophylactic measures.

NIAID intramural scientists and scientists in industry have grown hepatitis A virus (HAV) in tissue culture systems and produced live but weakened (attenuated) virus strains. Vaccines made from these strains were tested for safety in animal models and are now in human trials. NIAID intramural and industry scientists have cloned the entire genome of HAV and sequenced it. The regions of the genome encoding the surface antigens have been identified, and proteins produced by expression of these genes are being explored as potential vaccines. In addition, candidate antigens consisting of synthetic peptides have been shown to be antigenic, and their ability to protect against infection and disease will be studied.

Non-A, non-B hepatitis (NANB) accounts for about 90 percent of the transfusion-related hepatitis and 20 percent of the general hepatitis seen worldwide. NANB infections, like those of HBV, can progress to chronicity and sequelae such as cirrhosis but have not been associated with liver cancer. The causative agent(s) of NANB has not been identified and remains a perplexing problem. The chimpanzee is the only available model for studying this disease, since NANB does not grow in tissue culture cells or infect other animal species. Recently NIAID intramural scientists have shown that NANB is a lipid-enveloped virus with a RNA genome; its physical size is also now known. Work by NIAID scientists indicates that treatment of plasma derivatives with lipid-destroying agents may prove useful for eliminating NANB. Studies are under way using recombinant DNA technology to obtain clones of this virus. The work has been aided by the development of a monoclonal antibody that detects NANB virus in liver specimens. The monoclonal antibody is being used to study NANB infection in animal models and in human samples.

Monoclonal antibodies have been developed for facilitating epidemiologic investigations of the vaginal parasite, Trichomonas. Differences were demonstrated bet~~ween tri~~chomonas strains isolated from women in New York City, Baltimore, and Seattle. Rapid, reliable diagnostic methods are now feasible using the monoclonal antibody technique.

Two NIAID-supported clinical trials are studying interferon treatment of warts caused by papillomaviruses. Laryngeal papillomatosis (warts in the larynx) is quite rare, but when it occurs it is frequently associated with genital warts in the mother, suggesting acquisition during the birth process. The warty growths in the larynx can obstruct the airway, and surgery is the only currently available treatment. With aggressive disease, it must be repeated as frequently as every few weeks. The NIAID is currently conducting a large controlled study of interferon treatment of children with laryngeal papillomatosis; 123 children have been entered into the study.

Clinical evaluation of interferon for condyloma acuminata (genital warts) is progressing. The first placebo-controlled trial tested three different interferon preparations administered directly into the wart on the assumption that this would be the best approach for detecting activity but not necessarily the ideal route of administration. A follow-up protocol is currently under way in which several alpha interferon preparations are being compared in a placebo-controlled study design utilizing parenteral administration.

A polysaccharide vaccine for the prevention of the most important cause of bacterial meningitis in children, Haemophilus influenzae type b, was licensed in early 1985 for use in children two years of age or older. A modification of this vaccine (protein-polysaccharide conjugate) designed to make it immunogenic in younger children is being tested for efficacy in high-risk Eskimo children in Alaska.

A live attenuated varicella virus vaccine for the prevention of chickenpox in children with acute lymphocytic leukemia is expected to be licensed in 1986.

Some children are not being immunized against whooping cough (pertussis) because the standard vaccine is associated rarely with serious neurologic sequelae. These sequelae are thought to be related to unnecessary products in the vaccine. NIAID scientists have cloned and sequenced two genes of the pertussis organism. This could be an important step in the development of a clean vaccine.

Two groups supported by NIAID have been successful in developing candidate vaccines against the parasite causing malaria, *Plasmodium falciparum*; the vaccines will be tested for safety and antigenicity in human volunteers in the near future. Both vaccines are forms of a protein found on the surface of the sporozoite stage of the parasite. Another approach is to attack the merozoite stage of the parasite, which forms in the red blood cells (RBC's). A protein identified on the surface of the merozoite has been shown to bind to a specific receptor on the RBC surface. Further characterization of this antigen and others from the merozoite may lead to other malaria vaccine candidates.

Retrospective analyses of influenza virus isolates using monoclonal antibodies have shown that antigenic drift is a gradual process that takes place over a number of influenza seasons. Each winter many variants are identified but not all of the variants become significant in producing disease. By integrating the observations made in the field with laboratory studies of the molecular changes in the virus, scientists may soon be able to predict more accurately those variants with epidemic potential. This development has obvious implications for influenza vaccine manufacture since it will greatly simplify the process of antigen selection for the vaccine. More importantly, the antigen will be more likely to represent a true epidemic variant, and thus the effectiveness of the vaccines will increase.

Rotaviruses are the single most important cause of severe infantile diarrhea throughout the world. Field trials of two rotavirus vaccines derived from a calf and a rhesus monkey are under way in the United States, Europe, Africa, and South America. The calf strain has protected 88 percent of vaccinated Finnish children against severe rotavirus diarrhea. The rhesus strain, developed at the NIAID, has shown similar protective efficacy according to preliminary results from a trial in Maryland infants. A direct comparison of the rhesus and calf strain vaccines is currently under way in Navaho Indian infants in Arizona and in Peruvian infants under NIAID, USAID, and WHO sponsorship. A third promising candidate rotavirus vaccine strain, isolated from a calf, is being tested for safety and potency. Genetic engineering has enabled the production of alternate and hopefully more protective vaccine candidates, not yet tested in man, which contain important antigens located on the coat of human rotaviruses.

Molecular approaches toward understanding the pathogenesis of the bacteria causing Rocky Mountain spotted fever, *Rickettsia rickettsii*, and Lyme disease, *Borrelia burgdorferi*, have been initiated. Studies with extracts of *R. rickettsii* suggest that the principal protective antigen is a surface protein, which is being purified. In studies of *B. burgdorferi*, the genes coding for the two major outer membrane proteins have been cloned and characterized. This is the beginning of efforts to develop vaccines against these important spirochetes.

NIAID, through its outreach/technology transfer activities has sponsored conferences on AIDS for primary care physicians, health care workers and service personnel in Los Angeles, Chicago, Seattle, New Orleans, Miami, Boston and Houston. In addition, the Institute assisted with the International Conference on AIDS in Atlanta and supported a workshop on Pediatric AIDS in Florida. In addition to AIDS conferences, several conferences have been held around the country on immune system disorders, childhood immunodeficiencies, organ transplantation and systemic lupus erythematosus. Over 17,000 individuals have participated in the NIAID organized conferences.

Acquired Immunodeficiency Syndrome

Research on the acquired immunodeficiency syndrome (AIDS) has been a major research effort of the NIAID since the early description of this disease. Even before it was recognized as a new and distinct syndrome, patients were being evaluated by NIAID scientists for their unique and perplexing immune deficiency. With the realization that this disease was an infectious disease of the immune system which predisposes to additional, usually fatal, opportunistic infections and tumors, the NIAID has steadily increased its involvement and commitment of resources. The request excludes $67,731,000 for AIDS, which are under the single AIDS appropriation in OASH. Comparable amounts for 1986 are $25,903,000 and for 1985 $23,273,000.

The NIAID research efforts on AIDS, which were initiated primarily in the intramural program, have expanded, not only in the intramural program but also in extramural programs. The description of these efforts in this section include both intramural and extramural projects and, therefore, will not be addressed in subsequent program narratives. Moreover, these plans are contingent upon the assumption that funds appropriated for AIDS are made available to the NIAID to support noncompeting, ongoing, competing and new projects.

Studies to define the natural history of the disease and better understand its epidemiology are being supported in the United States as well as internationally. To elucidate the natural history of AIDS in homosexual men, investigators recruited over 1,000 volunteers without AIDS in each of five cities and are following them prospectively in order to study the role of various factors in the development of early manifestations of infection with the AIDS virus and subsequent disease. Data were collected initially, and continue to be at semiannual intervals, on lifestyle, medical history and pertinent physical signs. Body fluid samples are taken, stored and assayed for HTLV-III virus and antibody. Valuable information on transmission, on the significance of HTLV-III antibody and of viral isolation on outcome of disease, and on possible co-factors in disease development, should come from these studies.

A variety of agents with in vitro activity against the AIDS virus are currently being studied in the intramural program. Among them are Suramin, HPA-23 and Foscarnet. In addition, studies are under way to evaluate agents or procedures for their value in reconstitution of the immune system (i.e., interleukin-2, interferon and bone marrow transplantation).

Major problems in AIDS patients are the opportunistic infections that often are responsible for death. Through a number of contract-supported extramural projects, investigators are attempting to develop improved treatments for a number of these opportunistic infectious agents including cytomegalovirus, *Pneumocystis carinii*, *Candida albicans*, and *Mycobacterium avium-intracellulare*.

Among the projects being considered for support in FY 1987 are the continuation of the efforts described above along with continuation of new efforts developed with additional AIDS funding received in 1986. These areas include an expansion of international natural history and epidemiology studies in Africa, the Caribbean and in Asia. Studies are also planned on the role of co-factors and possible genetic/racial factors in the acquisition of infection and development of disease.

The NIAID, in collaboration with the National Cancer Institute (NCI), has developed a comprehensive program for the development and clinical evaluation of agents and procedures for treatment of AIDS, ARC and opportunistic infections. The program involves joint NCI-NIAID grant-supported National Cooperative Drug Discovery Groups, which will use modern technology to discover and create new candidate anti-HTLV-III drugs and the establishment of NIAID contract-supported screening units to evaluate candidate drugs for in vitro anti-HTLV-III activity. Preclinical testing in animals will be performed by the NCI. Evaluation of drugs for further testing in clinical trials is being done by the joint NCI-NIAID Drug Selection Committee that has non-Government expert representation. Phase I and phase II clinical testing will be carried out in a number of AIDS Treatment Evaluation Units to be established throughout the country, and including a variety of populations, with support via NIAID R&D contracts. These units will evaluate candidate agents against HTLV-III, agents and procedures for immune reconstruction and agents for treatment of opportunistic infections. Future efficacy trials will be done either through a network of these units or through new contracts for multi-center efficacy trials. These units will allow evaluation of treatment regimens to proceed much more quickly than is now possible and will allow a much larger number of AIDS and ARC patients access to well-designed and well-managed treatment studies.

While NIAID vaccine development efforts are still in the laboratory phase, the NCI is currently evaluating for safety and antigenicity in animals candidate vaccines made by extracting antigens from whole virus. When candidate vaccine materials are ready for human studies, phase I clinical evaluation for safety and immunogenicity will be performed in existing NIAID-supported vaccine evaluation units. Additional vaccine evaluation units and efficacy trials will be added in future years as needed.

The pathogenesis of infections caused by mycobacteria and fungi--important causes of opportunistic infections in patients with AIDS--will receive increasing attention. Recent studies indicate that gamma interferon appears to be the key T cell-produced lymphokine responsible for activating human monocyte-derived macrophages to kill intracellular pathogens. Also, T cells from AIDS patients with opportunistic infections fail to generate gamma interferon in response to specific microbial antigens. AIDS patients with infections caused by Mycobacterium avium-intracellulare typically remain bacillemic or have heavily infected tissues at autopsy despite conventional antimycobacterial therapy. In addition, it has been demonstrated that the T cell defect of these patients extends to absent or markedly impaired T cell-proliferative and gamma interferon generating activity in response to stimulation with specific mycobacterial antigens.

The NIAID has supported very successful outreach/technology transfer efforts aimed at providing information on AIDS to primary care physicians, health care workers and service personnel. A number of conferences have been held in major cities around the country which have, in all cases, been oversubscribed and very well received. It is planned to continue these activities as well as to develop workshops on AIDS for presentation, as requested, at national meetings of professional and lay organizations. Special efforts are also planned to develop new conferences and materials on the latest knowledge of the disease and patient management and care.

National Institute of Allergy and Infectious Diseases

Immunology, Allergic and Immunologic Diseases

1987 Authorization: Indefinite

Budget Authority:

1986 Appropriation	1986 Available after sequestering	1986 Revised Estimate	1987	Increase or decrease
$117,287,000	$112,376,000	$111,761,000	$106,473,000	-$5,288,000

Purpose and Method of Operation

The Immunology, Allergic and Immunologic Diseases Program supports research studies and research training on the structure and function of the immune system and its role in health and disease. Emphasis is placed on disorders of the immune system, such as asthma and other allergic diseases, congenital and acquired immune deficiencies, and immunoregulatory imbalances. Areas of concern also include natural mechanisms of disease resistance and cell-mediated immunity; drug-induced immunosuppression and other drug reactions; formation of antigen-antibody complexes in tissue, and their destructive pathologic consequences; autoimmune diseases; chronic disorders such as systemic lupus erythematosus, rheumatoid arthritis, and certain types of skin and kidney diseases; blood vessel conditions that impair the circulatory system, such as vasculitis; and a diverse group of diseases involving immunopathologic mechanisms affecting the metabolic, nervous, pulmonary and other systems in the body. Special consideration is being given to transplantation immunology, particularly to the mechanisms and prevention of graft rejection and graft-versus-host disease.

The major focus of this program is to develop new, fundamental knowledge of the immune system and its disorders through research project grants to individual scientists and through program projects to collaborative groups. The program project grants are focused on multidisciplinary studies of the biology of the immune system, mechanisms of immunologic diseases, and transplantation immunology.

A smaller but vital segment of this program focuses on two research centers programs: Asthma and Allergic Disease Centers (AADCs) and Centers for Interdisciplinary Research on Immunologic Diseases (CIRIDs).

AADCs foster collaborative approaches that integrate basic concepts in immunology, genetics, biochemistry, and pharmacology into clinical investigations. It is believed that translation of current immunologic concepts and methods to clinical studies will lead to an understanding of the pathophysiologic, biochemical, and immunologic mechanisms of asthma and other human allergic disorders. Objectives of this program are: to encourage collaboration between basic and clinical scientists; to provide research environments favorable for such interaction; and to implement clinical application of adequately tested research findings and procedures. The centers have facilities and personnel capable of designing long-term approaches either to the investigation of one or more major allergic disorders or to basic mechanisms of human allergic disease.

CIRIDs are organized to accelerate the clinical application of new knowledge of the immune system. Their programs integrate and coordinate research projects in immunology that are being pursued in clinical specialties (e.g., dermatology, pulmonary medicine, hematology, nephrology, rheumatology, infectious diseases, and otorhinolaryngology) with those in the basic biomedical sciences (e.g., immunobiology, immunochemistry, microbiology, virology, genetics, biochemistry, pharmacology, physiology, and pathology). A special feature of these centers is dissemination of information to physicians and patients through special projects and activities, such as recruitment and training of clinical investigators, demonstration programs, assessment of the regional socioeconomic impact of immunologic and allergic diseases, evaluation of new treatment modalities, application of promising investigative findings, and continuing medical education of practicing physicians.

As basic research approaches its final stages, research and development contracts play an integral role in this program. They are used to develop specific applications of research findings to the prevention, diagnosis, and treatment of disease and to solutions of health problems that are relevant to the basic mission of the Institute. Contracts are also used to produce and distribute research reagents and reference standards such as tissue-typing sera, hybridoma cell lines, and other materials to investigators working on transplantation research, genetics, and other biologic aspects of the immune system. To serve the scientific community, the Program also contractually supports computer-based systems for storage and retrieval of data concerning the molecular structure of antibodies, bone marrow transplantation, and hybridoma cell lines and their products.

To assure the influx of new investigators into immunology research, including allergic diseases, the program supports the research training and career development of laboratory and clinical scientists.

Rationale for the Budget Request

The 1987 budget estimate of $106,473,000 for immunology, allergic and immunologic diseases represents a decrease of $5,288,000 from the 1986 estimate. The requested funds will be used primarily for research project grants to fund approximately 587 awards, a decrease of 3 from 1986. Fourteen noncompeting research centers will be supported at negotiated reductions of about 30 percent compared to full funding in 1985 and reductions of 7 percent in 1986; and 27 research career awards will be funded. Approximately 170 full-time training positions will be supported, and funding will be provided for 14 research and development contracts.

Disorders of the immune system continue to be major health problems; asthma and allergic disease alone are known to affect at least 40 million Americans with socioeconomic impacts costing in excess of $4 billion per year. Asthma and severe allergic reactions including anaphylactic shock, adverse drug reactions and bee stings are documented causes of death. In addition, the chronic nature of allergic illness leads to restricted activity, school absenteeism, and loss of work and income. Other chronic diseases mediated by disorders of the immune system--such as systemic lupus erythematosus, rheumatoid arthritis, juvenile diabetes, some forms of nephritis, thyroiditis and vasculitis--require indepth study to dissect and define causative factors, immunopathologic mechanisms and methods to restore cellular elements and functional balance. Advances in the study of genetic mechanisms have furthered research approaches to the study of many diseases and have changed organ transplantation from a research activity to a clinically important surgical practice.

Program plans for 1987 are primarily concerned with four areas: (1) the structure and basic biologic function of elements of the immune system; (2) asthma and the classic allergic diseases of hay fever, urticaria and atopic dermatitis (eczema) and other disorders arising out of hypersensitive immune responses that accompany adverse reactions to drugs, foods, pollutants or insect stings; (3) genetic techniques for the treatment of hereditary immune-mediated diseases and for the prevention of rejection of organ transplants; and (4) immunologic diseases with special emphasis on defining the immunopathology of inflammation and cell dysfunction and their clinical manifestations.

Materials that have been employed in the matching of organ transplant donor and recipient pairs can be applied to clinical procedures designed to manipulate immune responsiveness in disease. Such reagents can aid in the diagnosis of a variety of immunologic diseases such as diabetes, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, and systemic lupus erythematosus. Advances in leukemia treatment and immune system reconstitution through bone marrow transplantation will be facilitated by further development of these reagents. To facilitate the application of molecular genetic techniques required to meet this objective, NIAID will participate in the planning and implementation of histocompatibility workshops.

Immunocompetent cells are able to distinguish foreign from self tissue through the recognition of cell surface molecules acting as histocompatibility/transplantation antigens. Extensive clinical trials are in progress based upon the use of monoclonal antibodies to destroy cellular elements of the immune system responsible for rejection phenomena in kidney and bone marrow transplantation.

Monoclonal antibodies prepared against surface markers on these cell lines have been used to modulate the immune response in animal models and in man and to study the characteristics of the critical surface markers including the T cell receptor. Some of these surface marker molecules are now being isolated and their chemical structures determined. The cells which mediate rejection do so both by direct cellular action and through the mediation of soluble secretions of certain lymphocytes known as lymphokines. Manipulation of lymphokine production is being further addressed as a means to regulate graft survival.

As long as the need for organs exceeds the supply, the effectiveness of organ preservation will remain a major factor affecting organ transplant success. Much injury to organs is caused by highly toxic metabolic products. This injury can be blocked by agents that prevent the generation, or interfere with the action, of these metabolites. Studies in animal models have confirmed the usefulness of these reagents and will allow for further evaluation in humans.

Monoclonal antibodies are being employed in numerous ways in clinical and research laboratories. For example, these antibodies are being used for rapid, precise diagnoses of infections and certain types of cancers, for clinical assays of enzymes and hormones, and for efficient purification of many substances. Many hybridoma cell lines, each producing a specific monoclonal antibody, are being developed in scores of different laboratories in the United States and in foreign countries. Consequently, there is a need for a repository and distribution center to ensure the availability of these extremely valuable cell lines. In an effort to fill this need, contractual arrangements between NIAID and private institutions have been initiated. In addition, maintenance of a hybridoma registry or "data bank" has been initiated so that detailed information about every known hybridoma can be stored in easily retrievable form.

Monoclonal antibodies have great potential in the treatment of human disease. Attempts are being made to join them to toxins leading to the ability to selectively kill specific cells. This approach could prove useful in producing monoclonal antibodies applicable to the treatment of severe infectious and autoimmune diseases, the reduction of immunologic rejections of organ transplants and the elimination of tumors.

Newly generated data from NIAID epidemiologic studies reveal an alarming change in the pattern of asthma. Since 1979, there has been an annual increase in U.S. mortality rates due to asthma. Hospitalization rates for asthma have also been increasing since 1972. While this figure includes all age groups, the data are especially impressive among children, where hospitalizations for asthma have increased 4-fold from 40 per 100,000 to 160 per 100,000 annually. Asthma has become the leading cause of admission in a number of children's hospitals in the United States.

Our knowledge of the causes and pathogenesis of asthma and allergic disorders is increasing rapidly, and it is evident that several areas offer exceptional opportunities for the development of improved methods of diagnosis, treatment and prevention. Among the research areas, priorities include specific studies on allergic and inflammatory chemical mediators and pathways such as: 1) the effect of Omega-3 fatty acids, which are present in fish oil enriched diets and have anti-inflammatory actions, in the prevention and treatment of asthma and allergic inflammatory disorders; 2) the role of naturally occurring neuropeptides in the production of asthma through their actions as neurotransmitting agents; 3) the design and development of new pharmaceutical agents to inhibit the cellular release of histamine, leukotrienes, platelet-activating factor and other chemical mediators of inflammation responsible for hypersensitivity reaction; 4) the chemistry of antigens that function as allergens; 5) the pathophysiologic mechanisms of allergen-induced respiratory tract, gastrointestinal and skin diseases resulting from mast cell discharge; and 6) the development of agents to stabilize mast cells and prevent the release of histamine and related chemical mediators of inflammation.

The effects of certain food additives, air pollutants and commonly used pharmaceuticals in the production of severe asthma and life-threatening anaphylactic shock reactions are being identified and reported with increasing frequency. Certain volatile chemical agents prevalent in industrial settings are also being increasingly recognized as causes of occupationally incurred asthma and immunologic lung diseases. Therefore, NIAID is planning to place increased emphasis upon investigations to identify those at risk both among general population groups and at work sites and to develop improved measures for the diagnosis, treatment and prevention of these disorders.

NIAID is concerned especially with the wide-spread problem of adverse drug reactions, many of which can be life-threatening. One such problem is the prevalence of severe reactions to radiocontrast dyes used in diagnostic X-ray studies. Approximately 9 million individuals in the United States are exposed to these agents in diagnostic studies of kidney, neurologic and cardiovascular diseases. Ten percent of these people can be expected to experience adverse reactions to the iodide-containing dyes.

Because such adverse drug reactions are responsible for considerable morbidity and potentially fatal situations, it is essential to go forward with new research efforts to identify those who are susceptible and at risk for fatal reactions. Tests are being developed to differentiate between those reactions that arise from truly allergic causes and those resulting from inflammatory sequelae of the activation of a series of interacting normal blood proteins known as the "complement cascade."

Procainamide hydrochloride is the most commonly prescribed agent for treating abnormal heart rhythms. Within one year of treatment, approximately 50 percent of patients taking this agent develop autoimmune-type antibodies similar to those characteristically found in systemic lupus erythematosus (SLE). Such immune responses can be detected in virtually all patients maintained on long-term use of this drug. Of those who develop this autoimmune response, some 10 to 20 percent actually develop clinical expressions of drug-induced SLE; of these as many as half will continue to have symptoms persisting even after drug withdrawal. Methods to predict those at risk of developing this serious drug reaction require continued investigation. Patients shown to exhibit slow natural inactivation of this drug by acetylation apparently develop autoimmune antibody responses more rapidly than those capable of rapid elimination by fast acetylation. Additionally, fruitful leads have been offered through indications of possible tissue specific type (HLA) associations with development of drug-induced SLE.

With regard to the dissemination of scientific information, NIAID will continue support of state-of-the-art, community activities and outreach programs utilizing the facilities and staff resources of the Asthma and Allergic Diseases Centers and Centers for Interdisciplinary Research on Immunologic Diseases. Such conferences, symposia and workshops, jointly sponsored by the Centers and professional and lay societies, have attracted large attendances and been very favorably received. Presentations by experts in the biomedical sciences working in areas relevant to Institute programmatic activities in asthma, allergic and immunologic diseases have been exceedingly useful in translating new research findings applicable to clinical issues in diagnosis, treatment and prevention. Following the established successful format, pertinent subjects to be covered during the next year will focus on neurologic and skin diseases caused by disorders of the immune system, autoimmune diseases, and self-management of asthma programs.

Impact Data

Subactivities	1986 Appropriation	1986 Available after sequestering	1986 Revised estimate	1987
Asthma and allergy..	$24,261,000	$23,237,000	$23,109,000	$22,011,000
Immunobiology and immunochemistry...	41,047,000	39,327,000	39,111,000	37,260,000
Clinical immunology & immunopathology.	24,445,000	23,402,000	23,271,000	22,157,000
Genetics and transplantation biology...........	27,534,000	26,410,000	26,270,000	25,045,000
Total.........	117,287,000	112,376,000	111,761,000	106,473,000
Res. Proj. Grants				
Number	613	613	590	587
Amount	101,098,000	96,761,000	96,146,000	93,434,000
Research Centers				
Number	18	18	18	14
Amount	5,809,000	5,559,000	5,559,000	3,734,000
Other Research				
Number	32	31	31	31
Amount	2,036,000	1,949,000	1,949,000	2,025,000
Training 1/				
Number	220	210	210	170
Amount	4,968,000	4,762,000	4,762,000	4,028,000
Res. & Dev. Contracts				
Number	17	17	17	14
Amount	3,376,000	3,345,000	3,345,000	3,252,000
Total				
Amount	117,287,000	112,376,000	111,761,000	106,473,000

1/ Numbers are full-time training positions.

National Institute of Allergy and Infectious Diseases

Microbiology and Infectious Diseases

1987 Authorization: Indefinite

Budget Authority:

1986 Appropriation	1986 Available after sequestering	1986 Revised Estimate	1987	Increase or decrease
$172,031,000	$164,526,000	$163,628,000	$156,775,000	-$6,853,000

Purpose and Method of Operation

The Microbiology and Infectious Diseases Program supports research with the broad aim of improving health by controlling diseases caused by infectious or parasitic agents. Projects range from studies of microbial physiology and antigenic structure to clinical trials of experimental drugs and vaccines. NIAID also supports studies on the mechanisms of resistance to antibiotics as well as research dealing with epidemiologic observations in hospitalized patients or community populations. Investigator-initiated research focuses on all aspects of microbiology, with particular emphasis on human pathogens. Areas of inquiry in basic microbiology include molecular anatomy and function, genetics, chemical composition, and physiologic and biochemical processes. Studies in bacteriology build on these data to identify immunizing antigens and to examine mechanisms of infection, pathogenicity, and virulence as related to such problems as hospital-associated infections and mycotic and sexually transmitted diseases. Areas of inquiry in virology include molecular structure, genetics, synthesis and reproduction, characterization of viral proteins and nucleic acids, mechanisms of pathogenicity, latency or persistence, reactivation, transformation and development of antiviral substances. This basic information is then applied to studies of the epidemiology, prevention and treatment of such diseases as influenza, genital herpes, hepatitis and diarrhea. Areas of inquiry in parasitology include biochemical, immunological and epidemiological studies of these much more complex multicellular organisms, along with studies directed toward biological control of their insect vectors.

Approaches being taken toward the prevention of infectious diseases and their sequelae include: immunization with vaccines; immunoprophylaxis with specific immune globulins; chemoprophylaxis; environmental control; interruption of spread by control of vectors; and interruption of spread by prompt diagnosis and early treatment of index cases.

Of these approaches, immunization is one of the most effective. Accordingly, a Program for the Accelerated Development of New Vaccines was initiated in 1981 to exploit recent advances in knowledge of the immune system and of the molecular and cellular biology of infectious agents, and the development of recombinant DNA and cell-fusion technologies that greatly simplify the identification and purification of protective antigens.

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Ten diseases or disease categories caused by 17 different organisms were targeted for prevention by immunization with new or improved vaccines by 1991. These diseases are: Meningitis in infants (Haemophilus influenzae type b, group B streptococci), croup and pneumonia in infants and children (respiratory syncytial and parainfluenza viruses), whooping cough (Bordetella pertussis improved), influenza (live attenuated), diarrhea (cholera, typhoid, dysentery, rotaviruses), hepatitis (type A, type B - second generation), chickenpox, gonorrhea, genital herpes, and malaria.

To assist in planning, NIAID chose the Institute of Medicine (IOM) to develop a model decision process that could be used for establishing priorities among candidate vaccines, both now and in the future. The analysis for the United States assigned the highest priority to the following five vaccines in the order listed: Hepatitis B virus (HBV, recombinant DNA-derived), respiratory syncytial virus (RSV, live attenuated), Haemophilus influenzae, type b (Hib), influenza (live attenuated), and varicella (immunocompromised children). Internationally, the analysis assigned the highest priority to the following five vaccines in the order listed: Streptococcus pneumoniae (protein-polysaccharide conjugates), rotavirus, malaria (P. falciparum sporozoite), Salmonella typhi (typhoid), and Shigella (bacillary dysentery).

To perform phase I testing of candidate vaccines, the Program supports four vaccine evaluation units at the Baylor College of Medicine, Marshall University (West Virginia), University of Rochester, and Vanderbilt University. The units complement each other in that various population groups (i.e., infants, young adults, "at risk" individuals) are available at some units, but not at others. Further, some can perform studies under closed conditions or in day care settings, while others work primarily in open populations. To determine whether live bacteria and viruses have been appropriately attenuated for use in humans and if they induce protection against challenge, the Program supports an in-patient Center for Vaccine Development at the University of Maryland. In 1986, in collaboration with USAID, another unit is to be established for the testing of malaria vaccines.

The Program supports seven multidisciplinary projects in developing countries (International Collaboration in Infectious Disease Research) to promote collaboration between scientists in the United States and in the host country institutions, to exchange scientists, to provide field experience which otherwise would not be available to United States investigators; and, ultimately, to learn how to prevent, control, and successfully treat tropical diseases. The Program supports other multidisciplinary research units in the United States to address important problems and to maintain centers of excellence in essential disciplines. These include six units for the study of sexually transmitted diseases (STDs), three for tropical diseases, and two for fungal infections.

Basic, applied, and developmental research are supported through investigator-initiated research project grants, research career awards and other research grants, and research and development contracts. Research training is also supported.

Rationale for the Budget Request

The 1987 request of $156,775,000 for microbiology and infectious diseases represents a decrease of $6,853,000 from the 1986 estimate. Because progress in infectious disease control is dependent on basic knowledge, the major funding is devoted to individual investigator-initiated research project grants. The requested funds will be used to fund approximately 1,012 such awards, a decrease of 6 from 1986. Forty-one research career program awards will be made, and approximately 205 full-time training positions will be supported. A total of 33 research and development contracts will be supported.

Program plans for 1987, along with expected accomplishments are concerned with five general research areas--molecular microbiology, pathogenesis of bacterial and viral diseases, parasitic diseases, clinical and epidemiologic investigations, and vaccine development--and with three specific research areas--infections of the respiratory, gastrointestinal, and genito-urinary systems, particularly STDs.

Research in molecular microbiology seeks to learn more about small pieces of DNA known as plasmids that are found in bacteria. These carry numerous factors that lead to resistance to antibiotics. For example, bacteria of different genera isolated at nine medical centers in the United States and at one center in Venezuela, during the first decade of gentamycin usage, carried a specific gentamycin-resistance gene on the same transferable plasmid. Continuing studies will focus on the nature of plasmids and their transmission.

Studies of the toxic shock syndrome (TSS) will continue to examine the role of toxins produced by strains of Staphylococcus aureus. Strains isolated from patients with TSS manufacture a characteristic protein, but the role of this protein in the pathogenesis of the disease is not certain. This toxic shock marker protein (TSMP) has been purified and is found to be a potent inducer of interleukin-1 (IL-1) production by human monocytes. Many features of TSS suggest that induction of IL-1 by TSMP in vivo may play a central role in the elaboration of this disease.

An animal model developed in mice, using the pathogenic fungus Cryptococcus neoformans will be used to study the pathogenesis and potential methods for control of this agent. The model will examine the role of macrophages and natural killer cells in the initial clearance from the lungs of intratracheally or intravenously administered C. neoformans. Macrophages appear to be critical in clearing intratracheally administered cells, while natural killer cells are more important against the intravenously administered cells. This is strong evidence that natural killer cells are important in killing circulating C. neoformans.

The occurrence of deep-seated fungal infections appears to be increasing. This is especially true in debilitated patients who are immunosuppressed from cancer therapy or from other treatment modalities that depress their immune systems. Standard treatment with the antifungal drug Amphotericin B requires hospitalization for intravenous administration and close monitoring for serious side effects such as impaired kidney function. Improved therapy for this group of infectious diseases is greatly needed. Controlled clinical studies are under way to evaluate a novel oral antifungal agent called Fluconazole. This new agent has been shown safe and effective in animal models and can be given orally to patients on an outpatient basis. It appears to be devoid of any serious side effects. During the next two years clinical studies are scheduled in patients with systemic histoplasmosis, blastomycosis, coccidioidomycosis and candidiasis.

African sleeping sickness is a tropical disease caused by a trypanosome and is transmitted by the bite of the tsetse fly. Invasion of the brain results in encephalitis leading to somnolence, coma and death. Suramin is an effective drug if used prior to brain invasion. Melarsoprol is effective in the brain but is very toxic. Studies of difluoromethylornithine (DFMO) have shown it to be curative in mice, and trials in humans in Africa have shown promising preliminary results. DFMO has been tested in combination with Suramin and found to exert a synergistic effect resulting in a 100-percent cure rate in chronic CNS infection. An even less toxic analog of DFMO has been synthesized and is being studied.

Filariasis occurs in the tropics in several forms, the best known being elephantiasis and river blindness (onchocerciasis). Diagnosis of the various types of filariasis is made by observation of the larval state (the microfilariae) in blood or tissue. Identification of species is often difficult, especially in the vector where human parasites may be mixed with numerous animal filariae. Recently, techniques of molecular biology have been utilized to develop a better diagnostic test. A genomic library of one parasite species has been screened to detect clones containing DNA sequences that are highly repeated within the parasite genome and do not cross-hybridize with DNA of other species. One clone was detected which was highly specific and sensitive. It correctly identifies infective larvae-containing mosquitoes that have been squashed on nitrocellulose paper and does not react with mosquitoes containing larvae of other species. The diagnostic potential of this system will be field tested in 1986 and 1987.

Transmission of herpes from mother to infant at birth is a serious threat to the newborn. New information on the prophylactic treatment of neonates with acyclovir indicates that, in cases where infectious virus has been detected in vaginal secretions, neonatal disease may be prevented if therapy is instituted sufficiently early after delivery.

Acellular pertussis (whooping cough) vaccines have been developed in Japan. Other vaccine manufacturers, both within and outside this country, are continuing their efforts to produce acellular vaccines that are very similar to the Japanese products. Several of these vaccines are expected to undergo safety and antigenicity studies in 1986 and 1987 in NIAID vaccine evaluation units. The anticipated recurrence of epidemic pertussis in Sweden has provided a setting for an efficacy trial of two acellular vaccines. This trial is now scheduled to begin in the first quarter of 1986. The large majority of funds for 1986 have been provided by USAID; funds for 1987 are to be provided by NIAID.

Live attenuated influenza A virus vaccines, administered intranasally, are being tested for safety in young children and in adults with cardio-pulmonary disease. If satisfactory, these trials need to be followed by extensive open trials to test vaccine efficacy during epidemics.

Live attenuated strains of the bacterium causing cholera with precise genetic lesions (missing sections of the genome that code for undesirable proteins) await testing in volunteers. If one of these is shown to be avirulent and protects volunteers against challenge, an extensive field trial in an endemic area should follow.

A live attenuated strain of hepatitis A virus is ready for initial testing in volunteers. If shown to be safe and immunogenic, this vaccine will require extensive safety and efficacy trials in both children and adults.

Two candidate vaccines for prevention of malaria will be tested for safety and immunogenicity in early 1986. If the volunteers show satisfactory antibody responses, the protective efficacy of the vaccines will be tested by allowing them to be bitten by infected mosquitoes. A satisfactory result will pave the way for efficacy trials in tropical countries.

Respiratory infections are the most common of all infections. Fortunately, most, such as the common cold, are not life-threatening; influenza and pneumonia, however, remain the fifth leading cause of death. Influenza virus epidemics occur regularly with their attendant high mortality and morbidity. The 1980-81 epidemic resulted in about 30-50 million cases of influenza and about 50,000 deaths. Respiratory syncytial (RS) and the parainfluenza (PI) viruses are also important causes of severe respiratory disease in the young and old. Approximately 10,000,000 cases of RS and PI virus infections occur annually.

A most important development has been the discovery of the molecular processes that underlie the variation in influenza viruses. This variability permits influenza viruses to escape neutralization by the host's immune system. Antigenic drift takes place in stages as mutations occur in the viral genes that code for the two principal influenza antigens, the hemagglutinin (HA) and the neuraminidase (NA). This process eventually yields a virus sufficiently different that it will escape the immunity built up in the population from earlier infections. If a virus with the neuraminidase and hemagglutinin not circulating in human populations is suddenly introduced, the effect can be catastrophic. The influenza pandemic of 1918 resulted in 500,000 deaths in the United States and perhaps 20,000,000 deaths worldwide, and was a result of this kind of change in the virus.

The host's immune response to the hemagglutinin is very important since antibodies to it are known to neutralize the virus and protect the host from reinfection. Research has identified the nature of the antigenic determinants of this protein. Investigators crystallized the hemagglutinin, making it amenable to x-ray crystallography and revealing its three-dimensional structure. A similar approach was also applied to the resolution of the structure of the viral neuraminidase. Other scientists provided field specimens and determined, through the use of monoclonal antibodies and fine structure analyses of many different hemagglutinin molecules, where mutations were located on the three-dimensional structure which permit the virus to escape neutralization by antibody. These developments will be used to seek new approaches to the treatment, prevention and diagnosis of influenza infections.

Gastritis is the fourth most common diagnosis in general medical practice. In 1982, a new type of bacterium was discovered in the stomach of patients with symptoms of gastritis who had upper abdominal pain, bloating, nausea, and occasional vomiting. Since then reports from all over the world have confirmed the association of this organism, called *Campylobacter pyloridis*, with gastritis. Some reports have also shown an association of *C. pyloridis* with peptic ulcers. An association of the infection with gastric cancer has been postulated more recently. Current evidence favors the opinion that the organism causes the gastritis rather than the gastritis permitting the infection. This will be further studied in 1986 in volunteers who ingest the organism and who are then followed clinically. This could be followed by further basic and applied research on C. pyloridis and lead to rational therapy and management.

New organisms that cause gastroenteritis (diarrhea, nausea, vomiting, and abdominal pain) continue to be discovered. For example, a virus resembling rotavirus morphologically, but distinct from rotavirus by chemical and genetic analysis, has now been shown to be associated with diarrhea in infants and adults. Preliminary sero-surveys indicate that infection with this virus, called rotavirus-like agent (RVLA), is prevalent in Baltimore. We now know the virus has caused epidemic outbreaks of gastroenteritis in American hospitals and in otherwise healthy populations in China. A large number of cases of diarrhea have no known cause, and RVLA may be responsible for many of these. A new rapid viral diagnostic test has just been developed, which will help to elucidate the epidemiology of RVLA infections throughout the world. Should RVLA and related viruses be found to be important agents of gastroenteritis, efforts will be directed at developing vaccines and other strategies to protect against them.

Sexually transmitted diseases (STDs) are a major problem throughout the world. In the United States, cases of gonorrhea have shown a small, continuous decline, although approximately 900,000 cases were reported in 1984. Similarly, syphilis cases declined somewhat, but the total for 1984 was still nearly 70,000 cases. Of greater public health importance, however, are the estimated 3,000,000 chlamydial infections and 500,000 new cases of genital herpes. Pelvic inflammatory disease (PID) is the most serious and most costly complication of STDs affecting women. It is estimated that PID costs nearly $2 billion annually if account is taken of hospitalization and therapy, surgical costs for ectopic pregnancies and time lost from employment. Nearly 40,000 women annually are rendered sterile as a result of PID. In 1986, the program will request proposals for two additional STD Research Units to begin in 1987 with a major emphasis on PID.

Chlamydia have been implicated, along with gonococci, as a major cause of PID. Diagnostic tests for chlamydial infection have hitherto been performed in laboratories by highly skilled personnel using sophisticated tissue culture techniques. An improved rapid and inexpensive diagnostic test, using a monoclonal antibody coupled with a fluorescent dye, has been developed by NIAID grantees. Monoclonal antibody typing is simpler to perform and is more precise than other methods. Inadequate diagnosis and treatment increases the risk of PID and also contributes to spread of the infection to others. Use of the new test will improve diagnosis and speed treatment.

Monoclonal antibodies specific for antigens of the spirochete causing syphilis have also been developed. This monoclonal material, coupled to a fluorescent dye, has been used to detect the presence of the spirochete in clinical specimens from syphilitic patients. This method is as sensitive and specific as the standard darkfield microscopy, with potential for providing a more convenient and accurate diagnosis of genital ulcer disease (e.g., early syphilis) caused by the spirochete. Expanded studies will determine whether this new test should be recommended for general use.

Impact Data

Subactivities	1986 Appropriation	1986 Available after sequestering	1986 Revised estimate	1987
Bacteriology and virology..........	$71,779,000	$68,684,000	$68,283,000	$65,924,000
Molecular microbiology and parasitology......	62,632,000	59,937,000	59,583,000	57,599,000
Development and applications......	26,857,000	25,645,000	25,534,000	23,903,000
Clinical and epidemiological studies...........	10,763,000	10,260,000	10,228,000	9,349,000
Total.........	172,031,000	164,526,000	163,628,000	156,775,000
Res. Proj. Grants				
Number	1,057	1,057	1,018	1,012
Amount	147,708,000	141,370,000	140,472,000	136,509,000
Other Research				
Number	50	48	48	48
Amount	3,280,000	3,139,000	3,139,000	3,328,000
Training 1/				
Number	271	253	253	205
Amount	6,285,000	6,008,000	6,008,000	4,955,000
Res. & Dev. Contracts				
Number	42	40	40	33
Amount	14,758,000	14,009,000	14,009,000	11,983,000
Total				
Amount	172,031,000	164,526,000	163,628,000	156,775,000

1/ Numbers are full-time training positions.

Intramural Research

1987 Authorization: Indefinite

Budget Authority:

1986 Appropriation	1986 Available after sequestering	1986 Revised Estimate	1987	Increase or decrease
$51,566.000	$49,133,000	$49,133,000	$51,492,000	+$2,359,000
		(FTEs: 519)	(519)	(--)

Purpose and Method of Operation

The scientists, technicians, and support staff of the NIAID Intramural Research Program represent an important national resource dedicated to better quality of health care through research in the areas of infectious diseases and allergic and immunologic disorders. This research is performed within an organizational structure consisting of 14 laboratories in Bethesda and Frederick, Maryland, and in Hamilton, Montana. In addition, individual NIAID intramural scientists are collaborating with and physically located within facilities of the U.S. Army Medical Research Institute for Infectious Diseases, The Johns Hopkins University and the Ministry of Health, Kinshasa, Zaire.

The mission of the intramural program is: (1) to conduct basic and applied research on immunologic and allergic diseases, infectious diseases, and related clinical disorders; (2) to provide experts in each of these areas who can advise the NIAID, PHS, and DHHS; and (3) to provide training in both clinical and basic biomedical research for young scientists in the disease areas within the Institute's realm of responsibility.

The research programs include the disciplines of virology, bacteriology, mycology, tropical diseases, parasitic infections, immunology, allergy, and asthma. The NIAID intramural program has placed considerable emphasis on research to study the nature of, seek treatment regimens for, and develop vaccines against AIDS, the Department's number one public health research priority. A long-term major focus of the intramural program is the development of improved vaccines for the prevention of parasitic, bacterial and viral infectious diseases such as malaria, gonorrhea, pertussis, infant diarrhea, hepatitis, influenza and other respiratory diseases.

Rational for the Budget Request

The 1987 budget request for intramural research is $51,492,000 an increase of $2,359,000 over 1986. While this funding level reflects $2,951,000 for mandatory administrative increases offset by a program decrease, the request provides for continuation of most research programs, with emphasis on vaccine development and development of antiviral agents. Particular emphasis will be placed on AIDS research, both for prevention and treatment of the infection and reconstitution of the compromised defenses resulting from the disease.

Recombinant vaccinia viruses that can protectively immunize experimental animals against respiratory tract infections have been constructed. A recombinant vaccinia virus that expresses the influenza virus hemagglutinin gene stimulated a humoral and cell-mediated immune response in experimental animals and protected them against lower respiratory tract infections. Another recombinant vaccinia virus that expresses the influenza virus nucleoprotein primed mice for cytotoxic T cell response that was directed against target cells infected with all human influenza virus types.

Respiratory syncytial virus is the leading cause of lower respiratory tract infection in infants. A recombinant vaccinia virus that expresses the respiratory syncytial virus glycoprotein protectively immunized rats against lower respiratory tract infection with respiratory syncytial virus.

Vaccinia virus vaccines have also been made with herpesvirus and hepatitis B virus; these have been tested in animals and are now being tested in man. Other genomes of pathologic agents that are being put into the vaccinia vector include malaria, rabies and leukemia retroviruses.

Malaria is still a leading cause of morbidity and mortality in the world today. Drug treatment and mosquito control have not kept malaria in check, indicating a clear need for a vaccine. Through modern biotechnology, a unique technique was developed by NIAID scientists that excised whole discrete genes from the malaria genome, leading to the development of a recombinant DNA vaccine. The vaccine has been produced and field trials will begin shortly.

In studies of host response to viral infections, a significant advance has been made by intramural scientists in understanding the pathogenesis of slow virus infections. Scrapie is a slow virus that causes an infection in sheep and goats similar to slow virus diseases such as Creutzfeldt-Jakob disease and Kuru in man. The virus is markedly resistant to agents that inactivate most viruses, and the disease causes no detectable host immune response. The intimate association of scrapie with host protein may account for many of its unusual features. NIAID intramural scientists have established high-titered, scrapie-infected, tissue culture cell lines. To obtain pure viral material, researchers cloned the scrapie prion protein gene. The cloned gene was found to be expressed as messenger RNA in brain tissue of both scrapie-infected and uninfected mice and hamsters. The prion protein appears to be a normal protein of the central nervous system. It is hypothesized that its accumulation in an aggregated fibril form in scrapie brain is secondary to tissue destruction induced by the scrapie agent. These studies open important areas for investigation of the pathophysiology of slow virus infections.

Sexually transmitted infectious diseases are a major source of morbidity in the United States. Genital herpes is a physically and psychologically debilitating infection. NIAID intramural scientists were the first to report an effective means of suppressing most outbreaks of genital herpes with acyclovir. Genital infection with Chlamydia trachomatis is now the most common bacterial sexually transmitted disease in the United States with estimates of up to 5 million infected individuals. Recent studies within the intramural program resulted in new rapid diagnostic tests that can be utilized in identifying and confirming C. trachomatis infections in both symptomatic and asymptomatic patients. It is now clear that there is a significant adverse association between C. trachomatis infection and outcome of pregnancy. With infection, there is increased incidence of spontaneous abortion, premature labor, low birth weight infants, and chlamydia pneumonitis in children born to infected mothers. Studies are in progress to better characterize the molecular constituents of chlamydiae membrane proteins with specific emphasis on defining the membrane antigens responsible for disease. Better treatment and control of this infection and development of a vaccine should result.

Gonorrhea remains a major problem in the United States and throughout the world. Current investigations by NIAID scientists have focused on the mechanism by which the infectious agent, *Neisseria gonorrhoeae*, invades the host. It has been shown that *N. gonorrhoeae* contains hair-like projections called pili, which are probably important in pathogenesis. The gene sequences controlling pilin, a constituent of mature pili, have been determined and changes in gene sequences have been shown to lead to a lack of pilin and thus pili formation. These basic studies may have important implications in terms of future therapeutic control or prevention of infection.

The development of a vaccine to prevent gonorrhea is an important priority. Two protein molecules (termed PI and PIII) extracted from the outer membrane of the gonococcus are potential vaccine candidates. NIAID scientists have investigated the interaction of these PI and PIII molecules with serum antibodies from hosts infected with *N. gonorrhoeae*. The results show that, in some circumstances, antibodies to PI and PIII can actually block rather than facilitate killing of the gonococcus. These results must be considered in vaccine development and may explain the difficulty in developing a successful gonorrhea vaccine.

Despite major advances in understanding the pathogenesis of sexually transmitted infectious diseases, in approximately 25 percent of patients the agent causing infection cannot be determined. NIAID investigators have isolated an agent, called *Mycoplasma genitalium*, which may cause many of these previously undiagnosable cases. Further studies are needed to precisely define the clinical importance of *M. genitalium* and, if it is important, to develop new therapeutic and preventive measures.

Arthropod-born (insect-transmitted) diseases include Rocky Mountain spotted fever and Lyme disease (arthritis). A recent discovery was that the etiologic agent of Lyme disease, transmitted by ticks, is the spirochete, *Borrelia burgdorferi* (named after the NIAID intramural scientist, Dr. Willy Burgdorfer, who identified the agent).

Although major emphasis in the NIAID intramural program is placed on the etiologic agents of infectious diseases, many groups are studying the basic elements of host defense. For example, fundamental studies are under way on the interaction of chemical mediators of inflammation with phagocytic cells (neutrophils and monocytes) important in microbial killing. These studies include unraveling the mysteries of phagocyte-directed locomotion (chemotaxis), phagocytosis and generation of toxic products such as hydrogen peroxide, hypochlorite and chlorine. Proper control of the release of these materials is essential to a normal inflammatory response; too little inflammation leads to a compromised host and recurrent infection, while too much inflammation leads to inflammatory disease. Patients with defects of these components of host defense have been studied intensively at NIAID. One group of patients has chronic granulomatous disease with absent hydrogen peroxide generation by phagocytes and recurrent life-threatening infections with certain bacteria and fungi. Phagocytes from some of these patients have been shown to lack cytochrome b, a specific component of the enzyme system responsible for hydrogen peroxide generation. Studies are under way to define the missing gene, with the eventual goal of transfection of a normal gene into the patients' cells.

As part of an effort to understand the pathogenesis of inflammatory diseases resulting from unchecked inflammation, NIAID scientists have developed a simple quantitative enzyme-linked immunoabsorbent assay (ELISA) for complement products that are potent mediators of inflammation. The ELISA assay was used to measure the concentration of fluid phase complement C5b-9 complexes. The complexes were not detected, or only poorly detected, in patients with non-inflammatory central nervous system diseases but were readily detected in the spinal fluid in 13 of 14 patients with acute Guillain-Barre syndrome and 16 of 21 patients with multiple sclerosis. The finding of complement complexes in the central nervous system of patients with Guillain-Barre syndrome and multiple sclerosis suggests that terminal complement components participate in the tissue-damaging processes in these diseases.

The recent discovery of an interaction between the immune, endocrine and nervous systems has potential importance in many clinical settings. As part of studies to understand these interactions, NIAID scientists have demonstrated that two neuropeptides effect the proliferation and differentiation of human B cells. Adrenocorticotropin hormone and beta endorphin increased the proliferation of activated B cells when present in culture. Future studies will characterize the nature of the interaction of these neuropeptides with human B cells and help clarify the potentially very important interactions of the immune-endocrine-neurologic networks.

Considerable emphasis in the NIAID intramural clinical program has been placed on understanding the basis of allergic diseases. Analyses of events in immediate hypersensitivity have focused on human and animal models of allergic responses, mechanisms of mediator action and pharmacologic approaches to allergic diseases. The areas under investigation include allergic rhinitis, anaphylaxis, urticaria, and systemic mastocytosis. One area receiving particular attention has been asthma.

Mast cells, the cells responsible for causing allergy, cause not only the classic signs of allergy (acute onset of sneezing, pruritis, erythema, whealing) but also initiate a prolonged inflammatory reaction. The reaction is due to "inflammatory factors," one of which has been purified, which attract neutrophils and eosinophils to the site of allergic reactions. This response evolves over 4-8 hours and is the mechanism for chronic asthma following allergen exposure. It is this inflammatory response that causes the irritability of the asthmatic airway--the irritability being the hallmark of asthma.

The acute inflammatory response seen in asthma is followed by a more chronic inflammation that may persist for days, weeks or even months after a single allergen exposure. Therapeutically, it is the chronic phase of the allergic response that responds to corticosteroid therapy. Use of corticosteroids in asthma may thus be designed to prevent or reverse airway inflammation and, as a consequence, airway irritability, with major effects on the prognosis and life-style of millions of Americans.

Up to 43 percent of Americans believe they are "allergic" to one or more foods. This belief derives from food-related symptoms, often quite vague and non-reproducible. Physicians have no reliable method to evaluate these mild symptoms or, even worse, those patients thought to have systemic allergic responses (anaphylaxis) from foods. Skin testing patients with food idiosyncrasies reveals that even in the group with dramatic "anaphylaxis-like symptoms," only half had positive skin tests. Employing freeze-dried foods in opaque capsules, oral challenge in the skin test negative group was universally negative. Provocation of the skin test positive group revealed about 50 percent responding to double-blind, placebo controlled challenges. Such data are useful for the proper evaluation and disposition of a large segment of the American public.

The highlights in the NIAID intramural research program discussed here are primarily clinical research. Behind these, however, is a very large foundation of basic research that constitutes the major part of the intramural research effort and without which advances for the benefit of the public health would not be possible.

Several laboratories in the NIAID are almost entirely devoted to basic research in the areas of immunology, immunogenetics, immunoregulation, cellular and humoral elements of the inflammatory process, molecular biology and microbial chemistry and physiology. That basic research is essential in providing the foundation for medical advances of an applied nature cannot be overemphasized.

The funding level requested for the intramural research program will provide for the continuation of high priority studies directed toward the development of vaccines and treatment regimens and for the development and clinical and basic science investigations of various infectious and allergic diseases. Efforts will continue to be directed toward the exploitation of the vaccinia virus approach to the development of a single vaccine against a variety of diseases, including AIDS, malaria, hepatitis, and infectious diarrhea. Development of a "clean" acellular pertussis vaccine for whooping cough will receive high priority as will study of the pathophysiology and treatment of allergic diseases. Other areas of emphasis will be development of new antiviral agents and new immunomodulators.

Research Management and Support

1987 Authorization: Indefinite

Budget Authority:

1986 Appropriation	1986 Available after sequestering	1986 Revised Estimate	1987	Increase or decrease
$16,054,000	$15,358,000	$15,358,000 (FTEs: 186)	$15,811,000 (186)	+$453,000 (--)

Purpose and Method of Operation

This activity provides the funds and positions that support the overall management and direction of the Institute. Included in this category are a wide range of managerial, scientific, and administrative functions ranging from program planning and scientific review to administrative and public affairs services.

The Office of the Director is concerned primarily with planning, evaluation and policy development. Administrative and managerial activities are located organizationally within the Office of the Director and staff offices, while program scientific activities are divided among the extramural programs (Extramural Activities Program; Microbiology and Infectious Diseases Program; Immunology, Allergic and Immunologic Diseases Program; and the most recent extramural entity, the Acquired Immunodeficiency Syndrome Program, which was established in fiscal year 1986.) These four extramural programs are responsible for reviewing, awarding and administering the Institute's substantial grant and contract activities with universities, medical schools, and other research organizations, providing guidance on scientific programs/projects, and for ensuring the dissemination of research results generated by these projects to the scientific community and the public.

Rationale for the Budget Request

The 1987 budget request for research management and support is $15,811,000 an increase of $453,000 over the 1986 level of $15,358,000. This funding level reflects $759,000 for mandatory administrative increases offset by a program decrease.

During 1987, major activities in this category will include:

° Continuation of efforts to maintain and streamline the ever increasing multi-media information dissemination activities being conducted by NIAID staff. These activities emphasize outreach in all the numerous diseases and disorders of concern to the NIAID. Efforts are conducted in collaboration with health professionals and voluntary associations, as well as with the various private sector elements that reach selected target audiences or at-risk groups, such as self-management techniques for individuals with asthma and allergic diseases.

° Maintenance of existing Institute processes aimed at streamlining and improving the various management review and approval processes and internal control mechanisms. These efforts would include continuation and refinement of recently instituted efforts in productivity improvement, contract management and administration, personnel management and administration, and manpower allocation and management.

° Continuation of efforts begun in 1986 to continually reassess the state of science in those areas within the Institute's purview. These efforts include the comprehensive review of scientific progress of ongoing projects, with special emphasis on the identification of areas of unusual scientific opportunity or interest. In this regard, particular attention will be focused on those areas ready for accelerated development that can bring into use improved means for preventing, diagnosing and treating diseases.

° Continuation of ongoing efforts to remain abreast of state-of-the-art automated data processing (ADP), and identification of those advances that can be utilized by the Institute to improve both the quality and efficiency of research. These efforts include continuation of the development of a comprehensive financial management data base to improve the accuracy and efficiency of managing and tracking financial plans and expenditures, and efforts to better utilize existing technology in the collection, processing and analysis of research data in both intramural and extramural projects. To the extent that funds allow, ongoing efforts to upgrade existing ADP hardware, software and communications will be undertaken.

° Continued use at reduced levels of task forces and outside advisory groups to assist the Institute in setting priorities and defining scientific opportunities. As part of the effort, the NIAID will establish a new scientific review committee, which will be responsible for assessing and recommending research projects on AIDS. In addition, the NIAID will continue to sponsor selected meetings, conferences, workshops, and symposia on high-priority research topics and issues, including areas of technology transfer and consensus development.

° Continuation of planning, policy development, and evaluation of collaborative research efforts with scientists in developing countries on basic and clinical research on diseases of international importance. The purpose of these collaborations will be to stimulate biomedical research in selected disease categories of interest to the Institute, with the ultimate goal of decreasing the morbidity and mortality rate in these countries. In 1987, special emphasis will be placed on collaboration and coordination of world-wide research efforts on AIDS. The incidence of AIDS in foreign countries is increasing, as it is in this country, and the differences and subtleties of AIDS as manifested in these countries are of critical importance and interest to U.S. researchers. To the extent that funds are available, the NIAID plans to capitalize on these important collaborations.

° Continue support of the NIH Recombinant DNA Advisory Committee. The NIAID has been charged by NIH with the responsibility of managing this effort, which has as its mission the oversight of the safety of recombinant DNA research. The NIAID plans to selectively support state-of-the-art and consensus development meetings and other scientific forums relating to recombinant DNA research.

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National Institute of Allergy and Infectious Diseases

Detail of Permanent Positions

	1985 Actual	1986 Estimate	1987 Estimate
ES-4	10	10	10
ES-2	2	2	2
Subtotal	12	12	12
GS-16	1	1	1
GS/GM-15	30	30	30
GS/GM-14	29	29	29
GS/GM-13	32	32	32
GS-12	34	34	34
GS-11	87	87	87
GS-9	103	103	103
GS-8	10	10	10
GS-7	88	88	88
GS-6	44	44	44
GS-5	48	48	48
GS-4	25	25	25
GS-3	8	8	8
Subtotal	539	539	539
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant surgeon General grade	1	1	1
Director grade	34	34	34
Senior grade	19	19	19
Full grade	5	5	5
Subtotal	59	59	59
Ungraded	42	42	42
Total permanent positions	652	652	652

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